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Effectiveness of trivalent and monovalent influenza vaccines against laboratory-confirmed influenza infection in persons with medically attended influenza-like illness in Bavaria, Germany, 2010/2011 season

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SUMMARY

We estimated the vaccine effectiveness (VE) of trivalent and monovalent influenza vaccines, respectively, against laboratory-confirmed influenza infections in patients with influenza-like illness who visited physicians participating in the Bayern Influenza Sentinel in Bavaria, Germany during 2010/2011. Swab specimens were analysed for influenza A(H1N1)pdm09, A(H3) and B by PCR. VE was estimated using the test-negative case-control study design and logistic regression. In total, 1866 patients (790 cases, 1076 controls) were included. The VE of trivalent vaccines administered in season 2010/2011 against laboratory-confirmed infection with any influenza virus, adjusted for age group, sex, chronic illness and week of arrival of the specimen, was 67·8% [95% confidence interval (CI) 39·2–82·9)]. The adjusted VE of monovalent influenza vaccines administered in season 2009/2010 against laboratory-confirmed influenza A(H1N1)pdm09 infection in 2010/2011 was 38·6% (95% CI −70·0 to 77·8). This is the first VE study conducted in Bavaria. We concluded that the trivalent influenza vaccines were effective in our study population.

Key words: Influenza (seasonal), influenza vaccines, vaccination (immunization), vaccine-preventable diseases, virology (human) and epidemiology.

INTRODUCTION

Starting in spring 2009, influenza A(H1N1)pdm09 spread across the globe and caused the first pandemic of the 21st century. In November 2009, the Bayern Influenza Sentinel system (BIS) was set up by the Bavarian Health and Food Safety Authority (LGL) to strengthen the regional surveillance of influenza activity in Bavaria through virological analysis of respiratory specimens from patients with influenza-like illness (ILI) presenting at sentinel physicians [1].

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The pandemic also induced the production of and immunization with monovalent influenza vaccines (MIVs) that had previously not been commercially available. In Germany, vaccinations began at week 44 (2009) and continued throughout autumn and winter 2009/2010. AS03-adjuvanted MIVs were mostly used. The coverage in the general population of Bavaria was estimated at 3·8% (95% CI 2·9–4·9) in April 2010 [2].

In spring 2010, the WHO recommended including pandemic influenza A/California/7/2009(H1N1) strain in trivalent influenza vaccines (TIVs) for use in season 2010/2011 together with the H3N2 A/Perth/16/2009 and B/Brisbane/60/2008 strains [3]. TIVs can mitigate the morbidity and mortality due to seasonal

influenza and the German Standing Committee on Vaccination (STIKO) recommends that, among others, persons aged $\geqslant 60$ years, pregnant women, those with underlying chronic respiratory, cardiovascular, neurological, liver or kidney illnesses, diabetes or immunosuppression as well as medical staff and elderly residents of care homes should be vaccinated against seasonal influenza [4, 5]. The health insurance companies in Germany reimburse all vaccinations recommended by STIKO, so the vaccinations are in effect free for persons belonging to the target populations. More than 15 different trivalent vaccines, both adjuvanted and not, were approved for use in Germany in the 2010/2011 season.

The influenza season in Bavaria corresponded to the German season, which started at the end of December 2010, was first dominated by influenza A(H1N1)pdm09 and then by influenza B (mostly Victoria line viruses) until the end of the season [6]. Most influenza cases, notified in accordance with the Protection against Infection Act, were reported in children aged <14 years [6].

As the composition of the trivalent vaccines is adjusted almost yearly to match the strains most likely to occur in the next season, the vaccine effectiveness (VE) must be estimated anew each season. Several methods can be used to estimate VE. Using persons who test negative for influenza as controls in a case-control study has been validated in modelling studies [7]. In Europe, the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network regularly estimates VE using this design [8, 9]. The network, however, does not include Germany. Therefore, we wanted to use the sentinel data acquired through BIS to estimate the VE of TIV in Bavaria, which with 12 million inhabitants is one of the largest federal states in Germany.

Furthermore, although MIVs had been proven to be effective against influenza A(H1N1)pdm09 during the 2009/2010 season, it was not clear whether it would remain effective in future seasons [10].

The specific objectives of our study were therefore to estimate VE of three types of vaccinations against laboratory-confirmed influenza infections in persons visiting sentinel physicians in Bavaria during the 2010/2011 season using the test-negative case-control study design: TIV administered in season 2010/2011, MIV administered in season 2009/2010, and both vaccines administered in the respective seasons.

METHODS

BIS

On a given day every week, BIS physicians took nasal or pharyngeal swabs or nasopharyngeal aspirates from the first two patients presenting with symptoms compatible with influenza. Specimens were collected using Σ-Virucult® (swab and transport medium) and analysed at LGL through real-time PCR as described previously [11]. The samples were first tested in parallel for influenza A (not strain-specific), A(H1N1)pdm09 and influenza B. Samples positive for influenza A, but negative for A(H1N1)pdm09, were further tested for influenza A(H1) and A(H3). The physicians also completed specimen collection forms that were sent to LGL together with the specimens. The forms included information about the patients' age, sex, TIV and MIV vaccination status and date of vaccination(s), symptoms and date of symptom onset, pregnancy, and presence of a chronic illness (respiratory disease, heart disease, diabetes), as well as date of specimen collection. The source of the information (measurements, medical records, vaccination booklets, patient disclosure/recall, etc.) was not documented.

Study population

We included all specimens that arrived at the virology laboratory at LGL during the influenza season of 2010/2011 [week 40 (2010) to week 15 (2011)] in the study. We excluded the specimens with missing laboratory results, those where the subtype could not be determined, those collected >7 days after symptom onset (to exclude possible false negatives), and those arriving at the laboratory >5 days after they were collected (as the sensitivity of the laboratory analysis could not be guaranteed) [12].

We further excluded specimens where the corresponding specimen collection form lacked information regarding trivalent vaccination status, monovalent vaccination status or date of either vaccination. Patients recorded as vaccinated with TIV before week 23 (2010) or with MIV before week 44 (2009) (when the respective vaccines were first available in Germany) were excluded, as were patients recorded as vaccinated with a monovalent vaccine after week 15 (2010) (i.e. the end of the 2009/2010 influenza season) [13]. We also excluded those vaccinated $\leqslant 13$ days before symptom onset, as the effect of the vaccination would be uncertain. For those where the

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date of symptom onset was missing, we excluded those vaccinated $\leqslant 63$ days before the sample arrived at LGL, assuming 14 days for immunity to develop, a 21-day margin and a maximum lag time of 28 days between symptom onset and arrival of the sample at the laboratory.

We used the EU case definition for ILI, defined as sudden onset of symptoms, and fever, chills, headache or muscle pains, and cough or sore throat [14]. Patients without ILI documented on the specimen collection form were excluded. We classified patients with a positive PCR test for influenza as cases, and those who did not test positive for any influenza virus as controls.

Descriptive analysis

We described and compared cases and controls with regard to age, sex, symptoms, underlying chronic illness, vaccination status, time between symptom onset and specimen collection (swab delay) and time between specimen collection and arrival at the laboratory (transport delay) using the χ^2 test or the Mann–Whitney test depending on the nature of the variable.

Estimates of VE

VE was calculated as 1 minus the odds ratio (OR) generated through logistic regression with laboratory-confirmed influenza infection as outcome and vaccination status as explanatory variable.

We estimated the VE of TIV only in season 2010/2011 against any laboratory-confirmed influenza infection, subtype A(H1N1)pdm09, A(H3) and B, respectively. The VE of TIV against any influenza infection was further estimated by age group (patients aged $\leqslant 14$, 15–59, $\geqslant 60$ years), and in those with and without reported chronic illnesses. All TIVs were analysed together, irrespective of vaccine brand. We restricted the analyses to specimens collected within active influenza periods, defined as consecutive weeks in which $\geqslant 10\%$ of sentinel specimens were positive for influenza viruses. The subtype-specific analyses were restricted to periods when the subtype was actively circulating.

We further estimated the VE of vaccination with MIV only in season 2009/2010, and of vaccination with both MIV and TIV in respective seasons, against laboratory-confirmed infection with A(H1N1)pdm09. The analysis was performed without regard to whether a vaccine brand had been documented on the specimen collection form.

All VE estimates were additionally calculated, adjusted by age group, sex, presence of a chronic illness and week of arrival of the specimen at the laboratory. The analyses were performed using Stata/IC 10.1 (StataCorp LP, USA).

RESULTS

Study population

During season 2010/2011, 141 physicians (95 general practitioners, 46 paediatricians) had agreed to participate in BIS and sent in at least one specimen. Specimens from 30 additional physicians were also analysed at LGL and included in the study. A median number of 14 specimens per physician (range 1–71) were sent for analysis.

In total, 2979 specimens were analysed. We excluded 19 (0·6%) specimens due to missing laboratory results, five (0·2%) specimens where the subtype was unclear, 45 (1·5%) due to swab delay and 62 (2·1%) due to transport delay (Fig. 1). We further excluded 184 (6·2%) patients where the seasonal vaccination status was missing, 365 (12·3%) patients with missing pandemic vaccination status, nine (0·3%) where the date of seasonal vaccination was missing, 10 (0·3%) where the date of pandemic vaccination was missing, three (0·1%) reported as vaccinated with seasonal vaccine before week 23 (2010), five (0·2%) reported as vaccinated with pandemic vaccine before week 44 (2009), five (0·2%) vaccinated with MIV in season 2010/2011, and three (0·1%) vaccinated $\leqslant 13$ days before symptom onset (Fig. 1). Finally, we excluded 398 (13·4%) patients that did not fulfil the EU ILI case definition, of which five were reported without any symptoms (Fig. 1).

Of the 1866 specimens included in the study population, 790 (42·3%) were PCR-positive and classified as cases. Of those, 652 (34·9%) were positive for A(H1N1)pdm09 and 129 (6·9%) for influenza B. A further nine specimens were positive for influenza A(H3).

There was no difference between cases and controls in median age, sex distribution or proportion with a chronic illness (Table 1). Of the 225 persons reported with a chronic illness, 106 had a respiratory illness, 18 diabetes and 52 heart disease. For 49 individuals the type of chronic illness was not reported.

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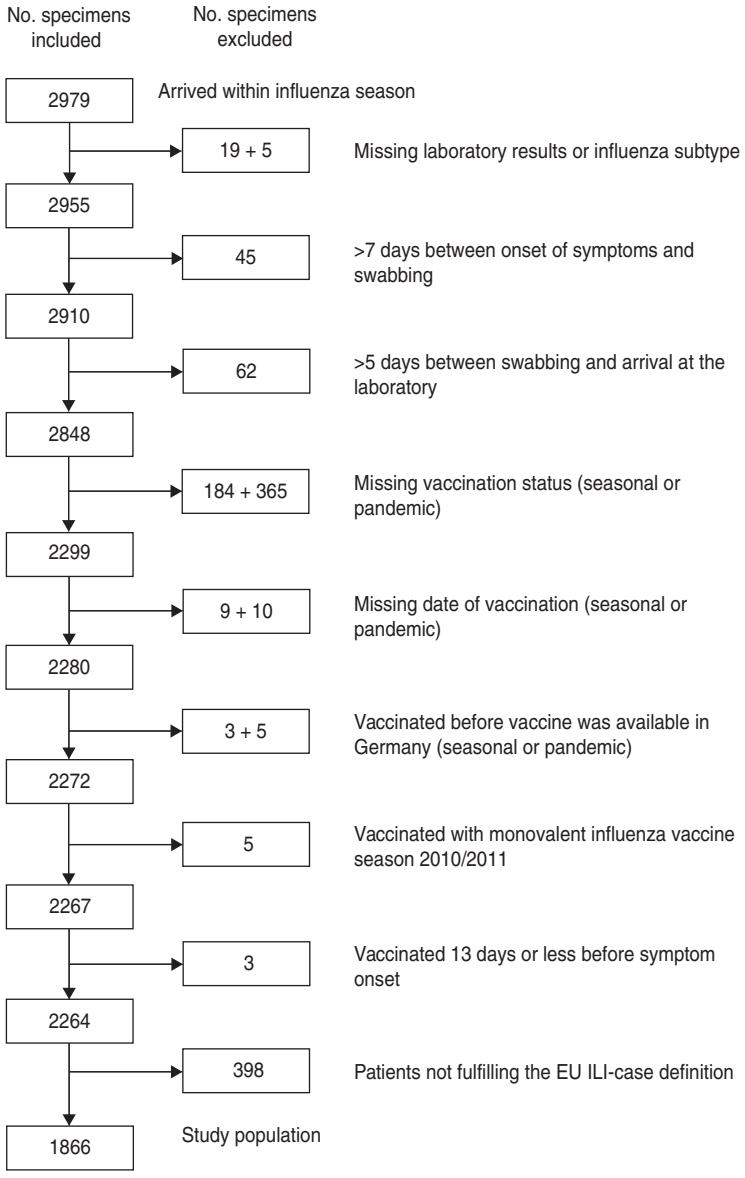

Fig. 1. Sequential exclusion of specimens collected through the Bayern Influenza Sentinel in the 2010/2011 season resulting in the study population ($n = 1866$), Bavaria, Germany.

Cases were more likely to have had fever or chills, cough, and muscle or joint pains than controls. However, controls were more likely to have had a sore throat. There was no difference in the number of patients with bronchitis or pneumonia in cases compared to controls (Table 1).

The vaccination status differed between cases and controls; controls were more often vaccinated with TIV than cases, whereas no difference was observed in the proportion vaccinated with MIV (Table 1).

The median time between symptom onset and specimen collection (swab delay) was 1 day for cases and 2 days for controls, but the proportion of specimens collected $\geqslant 3$ days after symptom onset did not differ significantly (Table 1). The median time between specimen collection and arrival of the specimen at LGL (transport delay) was 2 days for both cases and controls.

Vaccinated individuals

For 55/62 (89%) individuals vaccinated against seasonal influenza the vaccine brand was recorded in the specimen collection form. Ten different brands were

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Table 1. *Description of cases* (*influenza test-positive*) *and controls* (*influenza test-negative*) *in the study population, Bavaria, Germany 2010/2011*

	Cases ($N=790$)	Controls ($N=1076$)	P value
Median age (years)	22·8	23·0	0·336*
Age group (years), *n* (%)			0·162†
0–14	362 (45·8)	473 (44·0)	
15–59	387 (49·0)	523 (48·6)	
⩾60	18 (2·3)	44 (4·1)	
Missing	23 (2·9)	36 (3·4)	
Sex, *n* (%)			0·165†
Female	360 (45·6)	524 (48·7)	
Male	429 (54·3)	547 (50·8)	
Missing	1 (0·1)	5 (0·5)	
Symptoms, *n*/*N* (%)			
Fever or chills	754/780 (96·7)	957/1065 (89·7)	<0·001†
Cough	753/790 (95·3)	917/1072 (85·5)	<0·001†
Sore throat	523/755 (69·3)	804 /1012 (79·5)	<0·001†
Muscle or joint pains	674/750 (89·9)	844/992 (85·1)	0·003†
Bronchitis	320/755 (42·4)	442/1036 (42·7)	0·906†
Pneumonia	8/747 (1·1)	16/1022 (1·6)	0·374†
Pregnancy (women), *n* (%)			0·521†
Yes	5 (1·4)	4 (0·8)	
No	307 (85·3)	441 (84·2)	
Missing	48 (13·3)	79 (15·1)	
Chronic illness (any), *n* (%)			0·308†
Yes	97 (12·3)	128 (11·9)	
No	670 (84·8)	928 (86·3)	
Missing	23 (2·9)	20 (1·9)	
Vaccination status, *n* (%)‡			<0·001†
Not vaccinated	768 (97·2)	996 (92·6)	
TIV vaccination 2010/2011 only	14 (1·8)	48 (4·5)	0·001†
MIV vaccination 2009/2010 only	8 (1·0)	16 (1·5)	0·316†
Both vaccinations	0 (0·0)	16 (1·5)	<0·001†
Median swab delay (days)	1	2	0·059*
Swab delay ⩾3 days	173/757 (22·9)	250/1010 (24·8)	0·355†
Median transport delay (days)	2	2	0·826*

TIV, Trivalent influenza vaccine; MIV, monovalent influenza vaccine.
* Mann–Whitney test.
† χ^2 test.
‡ Persons with missing vaccination status were excluded.

mentioned and 11/55 (20%) were vaccinated with adjuvanted vaccines. Of those vaccinated, 27/62 (44%) had a chronic illness, compared to 184/1764 (10%) of the non-vaccinated ($P<0·001$). Those vaccinated were also significantly older than those who were not (median age 47·8 years *vs.* 16·2 years, $P<0·001$). However, having a chronic illness was also associated with older age; the median age was 34·1 years in those with a chronic illness compared to 15·5 years in those without such an illness ($P<0·001$).

The proportion vaccinated against seasonal influenza in children, adults and the elderly (where age was known) was 1·9%, 3·2% and 30·4%, respectively. The vaccination coverage was higher in those with a chronic illness than in those without (12·8% *vs.* 2·1%, $P<0·001$) and slightly higher in women compared to men (4·3% *vs.* 2·6%, $P=0·053$).

There was no difference in sex distribution or median age between those vaccinated with monovalent vaccines and those not vaccinated, but those aged ⩾60 years were almost eight times more likely to have been vaccinated than those aged <18 years [OR 7·6, 95% confidence interval (CI) 2·3–24·9, $P<0·001$]. Those with a chronic illness were also more often

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Table 2. *Crude and adjusted estimates of vaccine effectiveness (VE) of trivalent influenza vaccines against laboratory-confirmed influenza infections during periods of viral circulation in Bavaria, Germany, 2010/2011 season*

	Crude		Adjusted*	
	VE (%)	95% CI	VE (%)	95% CI
All influenza†	67·8	39·2 to 82·9	70·3	40·0 to 85·3
Age group (years)				
0–14	75·5	12·5 to 93·2	83·8	23·9 to 96·6
15–59	45·1	−25·8 to 76·1	57·2	−5·9 to 82·7
⩾60	88·5	0·5 to 98·7	92·4	−66·7 to 99·7
Chronic illness				
No	75·4	34·4 to 90·8	75·7	32·8 to 91·2
Yes	69·7	23·2 to 88·0	80·6	32·7 to 94·4
A(H1N1)pdm09	66·7	34·1 to 83·2	66·5	29·8 to 84·0
A(H3)	n.a.‡		n.a.‡	
B	40·6	−177·9 to 87·3	68·7	−197·7 to 96·7

CI, Confidence interval.
* Adjusted for age group, sex, presence of a chronic illness and week of arrival of the specimen at the laboratory.
† Includes infections with A(H1N1)pdm09, A(H3) and B.
‡ Not available because none of the cases were vaccinated.

vaccinated with MIV than those without such an illness (3·7% *vs.* 1·1%, $P=0·004$).

Influenza active period

The active period for influenza viruses overall was between week 49 (2010) and week 13 (2011) in Bavaria; 768/790 laboratory-confirmed cases were detected within this time period. The influenza A(H1N1)pdm09 active period lasted between week 49 (2010) and week 11 (2011) (637/652 cases detected within this period), and influenza B was active in weeks 9–13 (2011) (71/129 cases detected). All nine influenza A(H3) cases were detected between weeks 3 and 14 (2011).

Vaccine effectiveness of TIVs

The crude VE estimate of TIV against laboratory-confirmed infection with any influenza virus was 67·8% (95% CI 39·2–82·9) and the adjusted estimate 70·3% (95% CI 40·0–85·3) (Table 2). The VE estimates did not differ between age groups or between those with and without chronic illness. The crude VE estimate against A(H1N1)pdm09 specifically was 66·7% (95% CI 34·1–83·2) and the adjusted estimate 66·5% (95% CI 29·8–84·0) (Table 2). The VE estimates against infection with influenza B did not reach statistical significance (Table 2). None of the nine patients who tested positive for influenza A(H3) 2011 had been vaccinated with TIV.

Vaccine effectiveness of MIVs

The crude VE of MIVs administered in the 2009/2010 season against infection with influenza A(H1N1)pdm09 in the 2010/2011 season was 23·8% (95% CI −101·5 to 71·2) and the adjusted estimate 38·6% (95% CI −70·0 to 77·8).

Sixteen patients had been vaccinated with a monovalent vaccine in 2009/2010 as well as a trivalent vaccine in 2010/2011. None of these tested positive for influenza A(H1N1)pdm09.

DISCUSSION

Effectiveness of TIVs

In our study, we used the test-negative case-control study design to estimate the effectiveness of influenza vaccines. Some of the strengths of this study design are that a similar healthcare-seeking behaviour can be assumed for both cases and controls and that the outcome is unknown at the time of specimen collection and therefore does not bias the selection of study participants [15].

We estimated the adjusted VE of TIV in the 2010/2011 season to be around 70%, both overall and

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specifically against influenza A(H1N1)pdm09 and influenza B. Our point estimates were somewhat higher than the results from other European studies that employed the same study design [16–18]. However, since the specificity of our estimates was lower than in these studies, the results can still be considered similar.

Using the information on age and presence of chronic illnesses, we were able to adjust our estimates to these potential confounding factors. We were, however, not able to adjust the estimates for previous vaccinations against seasonal influenza. Because of the STIKO recommendations, it is possible that persons with chronic illnesses and those aged above 60 years had been vaccinated several times in previous seasons. Assuming that previous vaccinations would increase immunity in season 2010/2011, it would contribute to an overestimation of VE against influenza B in our study. The effectiveness against infection with A(H1N1)pdm09 would, however, not be affected because it was not included in TIVs before the 2010/2011 season. As most of the weight in the VE estimate of TIV against all influenza came from the effectiveness against influenza A(H1N1)pdm09, we do not believe that previous vaccinations against seasonal influenza influenced these estimates to a large extent.

Including patients vaccinated with a monovalent vaccine in the previous season would also have affected the VE estimate, leading to an overestimation of TIV effectiveness in this season. Therefore, those who had received MIV only or both vaccinations were analysed separately. However, it is possible that some persons were incorrectly classified as non-vaccinated, i.e. those forgetting receiving the pandemic vaccine where patient recall was the source of vaccination status. The argument supporting forgetfulness is that the entries concerning monovalent vaccinations in the specimen collection forms were missing eight times as often as the statements regarding seasonal vaccination. However, as monovalent vaccination coverage in Bavaria was low, we do not believe that this possible misclassification would have had a large impact on the estimates.

It is also possible that we underestimated VE. It is known that the test-negative case-control study design in itself tends to underestimate VE, especially when VE is high [7]. Furthermore, vaccination coverage in Germany in previous seasons has been $\sim$30% in adults aged 18–59 years, $\sim$15% in adults without chronic illnesses and $\sim$45–55% in those aged $\geqslant$60 years [19–22]. The coverage in 2010/2011 is reported to have been in the same range (M. Böhmer, personal communication, August 2012). The vaccination coverage in our study population was lower than this, both in adults in general and those aged $\geqslant$60 years in particular. If this discrepancy was the result of vaccinated persons less often seeking healthcare or being misclassified as unvaccinated it would also lead to an underestimation of VE.

Effectiveness of monovalent vaccines against influenza A(H1N1)pdm09

Since the pandemic, several studies have proved the long-term (6–12 months) persistence of influenza A(H1N1)pdm09-specific antibodies in both children and adults [23–28]. VE studies have, however, suggested that the residual protective effect 1 year after the pandemic was limited [16, 18]. A limited effectiveness in combination with a small number of vaccinated persons included in our analysis could explain why we were not able to provide statistically significant effect estimates for MIVs against infection with influenza A(H1N1)pdm09.

None of the patients in our study that received a monovalent vaccine in 2009/2010 and had additionally been vaccinated with a trivalent vaccine in 2010/2011 were PCR-positive for influenza A(H1N1)pdm09, suggesting that this combination of vaccines provided a high level of protection. These findings are in line with other studies [16, 18].

CONCLUSIONS

TIVs were effective against laboratory-confirmed influenza infection in medically attended ILI patients in Bavaria, Germany in the 2010/2011 season, whereas monovalent vaccines administered in 2009/2010 may only have provided limited protection against infection with influenza A(H1N1)pdm09.

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DECLARATION OF INTEREST

None.

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