Table 1 Demographics, immunogenicity and safety data of the study group

Demographics		**Nutritional status**	
Patients enrolled: 48			
Mean age: 14.4 years (range 8 months–26 years)			
M/F: 20/28		Patients<18 years (n=32):	mean HAP 25.1
F508del (37/48, 77.1%):	8 homozygotes		mean WAP 41.8
	29 heterozygotes		
Pseudomonas colonisation: 29/48 (60.4%)		Patients≥18 yrs (n=16):	mean BMI 21.9
Mean FEV_1: 86.5%±25.1			
O_2 therapy: 1 patient			

Immunogenicity*	**Baseline**	**21 days postimmunisation**
Patients assessed: 33		
CD4 T cell/µl (%)	1163 (42.3)	–
Geometric mean titre (95% CI)	40 (20–81)	582 (388–872)
Geometric mean ratio of HI titre (95% CI)	–	13.9 (6.9–26.7)
% Seroconversion (95% CI)	–	83 (60–91)

Safety			
Local reactions:	13/48 (27.1%)	Pain	12/48 (25%)
		Swelling/redness	7/48 (14.6%)
Systemic reactions:	12/48 (25%)	Fever	5/48 (10.4%)
		Myalgia	4/48 (8.3%)
		Headache	3/48 (6.3%)
		Fatigue	3/48 (6.3%)
		Chills	1/48 (2.1%)

*Immunogenicity was assessed according to the CPMP criteria: seroconversion was defined as prevaccination antibody titre of 1:10 or less and a postvaccination titer of 1:40 or more or a prevaccination titre greater than 1:10 and an increase in the antibody titre by a factor of four or more. Seroconversion rate was calculated as the percentage of patients that displayed seroconversion. Serum antibody titres were determined using the haemagglutination inhibition (HI) assay. Sera geometric mean titres (GMT) and ratios (as fold increase) in HI titres of day 21 to day 0 titres were also calculated.
HAP, height for age percentile; WAP, weight for age percentile; BMI, body mass index; FEV_1, forced expiratory volume in 1 s.

Focetria (Novartis) monovalent inactivated pandemic influenza vaccine corresponding to 7.5 µg of haemagglutinin (HA) antigen strain A/California/7/2009 (H1N1)v like strain (X-179A) MF59-adjuvanted between November 2009 and February 2010. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm on day 0. Blood samples were collected on day 0 and on day 21 to assess immunogenicity according to the Committee for Proprietary Medicinal Products (CPMP) criteria[5]; CD4 T cell counts were also assessed on day 0 to exclude immunodeficiency. Patients or their parents recorded in a diary card the onset and severity of solicited local and systemic reactions within 7 days after the vaccine administration.

We enrolled 48 CF patients with an average good pulmonary function and nutritional status. They showed normal CD4 T cell counts. All patients were assessed for safety and 33 of them for immunogenicity. There were no dropouts because of adverse reactions. The vaccine was well tolerated and no serious adverse events have been reported. All recorded symptoms were mild and short-lasting. The most frequent reported symptoms were local reactions. Seroconversion rate was satisfactory and met all the CPMP criteria. Demographics, immunogenicity and safety data are shown in table 1.

In conclusion, a single 7.5 µg dose of the monovalent A/H1N1 MF59-adjuvanted vaccine results in a high rate of seroconversion in CF patients. These data support the current influenza vaccination strategy. The vaccine is well tolerated and the frequency of adverse events is comparable with literature data regarding other influenza vaccines. However, we studied a small cohort of young patients with an overall good nutritional and lung status. In severe malnourished CF patients, supposed to have a decreased immune response, the vaccine may not have the same efficacy. Future prospectical studies are needed to evaluate the benefits of influenza vaccines on defined clinical outcomes.

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Influenza A/H1N1 in patients with cystic fibrosis in Italy: a multicentre cohort study

The clinical consequences of influenza are severe in cystic fibrosis (CF), but the impact of A/H1N1 virus infection remains poorly defined.[1 2] Pandemic influenza A/H1N1 started in Italy in September 2009 and CF patients were included among those at risk of complications and recommended to receive A/H1N1 vaccine. Better characterisation of the impact of influenza A/H1N1 in comparison with other flu-like illnesses in CF would provide a rational basis for antiviral treatment and vaccination strategies for the next flu season.

Within the Italian Cystic Fibrosis Society, we sent a questionnaire to 30 centres to collect follow-up data for all patients with influenza-like symptoms consecutively seen between November 2009 and March 2010. Realtime RTPCR test was performed to define A/H1N1 status.[3] Continuous variables are reported as medians, IQR (see online supplement for details of study methods).

Nineteen centres reported data from 127 patients: 68 were 'A/H1N1+ve' and 59 were 'A/H1N1–ve' for the RT-PCR test.

Symptom onset peaked during calendar week 45 in A/H1N1+ve patients, similar to the general Italian population,[4] whereas A/H1N1–ve patients showed a bimodal incidence peak at weeks 45 and 47 (online supplementary figure S1).

A/H1N1+ve patients tended to be younger than A/H1N1–ve patients (40% vs 58% aged ≥18 years; p=0.051), with no other differences in clinical characteristics or symptoms leading to presentation to centres (online supplementary table S1).

Table 1 Clinical course of influenza illness and major complications according to the results of influenza A/H1N1 testing

	A/H1N1+ve (n=68)	A/H1N1−ve (n=59)	All patients	RR (95% CI)	p
Duration of disease (days)*	5 (3−11)	10 (6−14)	7 (4−14)	−	0.002
Pulmonary exacerbation†	46 (67.6%)	47 (79.7%)	93 (73.2%)	0.85 (0.69−1.05)	0.127
Hospitalisation	47 (69.1%)	41 (69.5%%)	88 (69.3%)	1.00 (0.79−1.25)	1.000
Antiviral therapy‡	56 (82.4%)	7 (11.1%)	63 (49.6%)	−	<0.0001
Complications	10 (14.7%)	7 (11.9%)	17 (13.4%)	1.24 (0.50−3.05)	0.795
Permanent need for oxygen therapy	1 (1.5%)	0	1 (0.8%)	−	−
Respiratory failure	1 (1.5%)	1 (1.7%)	2 (1.6%)	−	−
Pneumothorax	1 (1.5%)	0	1 (0.8%)	−	−
Haemoptysis	2 (3.0%)	2 (3.4%)	4 (3.1%)	−	−
Atelectasia	0	1 (1.7%)	1 (0.8%)	−	−
Death	3 (4.4%)	1 (1.7%)	4 (3.1%)	2.60 (0.28−24)	−

*Among the 68 patients with A/H1N1 infection, duration of disease was 5 (3−9) days in the 56 patients treated with oseltamivir and 5 (3−11) days in the 12 patients who did not receive antiviral treatment (p=0.874).
†Among the 68 patients with A/H1N1 infection, pulmonary exacerbations occurred in 69.6% of patients treated with oseltamivir and in 58.3% of those who did not receive antiviral therapy (p=0.505).
‡Among the 68 patients with A/H1N1 infection, complications occurred in 17.9% of patients treated with oseltamivir and in none of those who did not receive antiviral therapy (p=0.189).

Oseltamivir (2−3 mg/kg/day as currently recommended) was administered to 82% A/H1N1+ve and 12% A/H1N1−ve patients. In the A/H1N1+ve group, treatment was started within 24−48 h from symptom onset upon virological confirmation. Oseltamivir was well tolerated and no treatment cessation was required. In one AH1N1+ve patient complications were associated with development of oseltamivir resistance.[5]

Clinical course and duration of disease are reported in table 1. In the entire CF patient population, shorter disease duration was seen in oseltamivir treated patients (5, 4−11 vs 10, 6−14 days; p=0.008), a difference apparently limited to the A/H1N1−ve subset.

During illness, 68% A/H1N1+ve and 80% A/H1N1−ve patients developed pulmonary exacerbations (p=0.127). Disease course was uncomplicated in 85% and 88% patients, respectively (p=0.639). Of note, immunosuppressive therapy for organ transplantation did not increase risk of complications in either group.

Four patients with severe pulmonary disease (3 A/H1N1+ve, 1 A/H1N1−ve) died of respiratory failure: none had been vaccinated and all had received antiviral therapy (online supplementary table S2).

No significant FEV_1 decline was observed in both groups after 1 and 6 months from symptom onset (online supplementary figure S2). In none of the cases, new isolation of *Pseudomonas aeruginosa* or *Burkholderia cepacia* complex was documented.

In conclusion, in a cohort of patients who consecutively presented to Italian CF centres for flu-like symptoms during the 2009 pandemic period, accurate diagnostic testing did not identify clinical characteristics specifically associated with A/H1N1 infection, the only exception being younger age in A/H1N1+ve patients. The use of a reliable identification method allowed appropriate treatment to be initiated.

Systematic collection of data at patient presentation and subsequent follow-up provided further information on A/H1N1 infection in CF, which will be useful to patients for the next influenza season.

Influenza A/H1N1 has no major impact in CF, but patients with poor clinical conditions due to the disease are exposed to substantial risk of complications and unfavourable outcomes. Annual vaccination for seasonal influenza and A/H1N1 influenza is recommended in CF, with continuing efforts towards higher vaccination coverage levels especially in adult subjects.

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The mortality of treated acute PE

I read with interest the editorial in *Thorax* entitled 'Identification of those at risk after acute pulmonary embolism'.[1] In the second paragraph, the authors state and reference the inpatient mortality for normotensive patients with acute PE as ~10%.

My concern is twofold. First it is that readers may surmise that the mortality of acute treated PE is as quoted, when in reality the all-cause out of hospital 3 month mortality of those with PE is 9% in the reference quoted. This level of mortality relates not just to the PE but to the co-morbidities, such as cancer, that this cohort frequently possess. Secondly, in clinical experience it seems a rarity that those even with a large clot burden identified on CT pulmonary angiography (CTPA) and without life-threatening co-morbidities do not improve their clinical state once treated with anticoagulation. Do the editors know of any studies that clearly identify the cause of death systematically in those with PE so that we can truly pick out the mortality associated with this diagnosis?