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## Influenza A(H1N1)v pandemic in the dialysis population: first wave results from an international survey

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### Abstract

**Background.** After the first cases of influenza A(H1N1)v in Mexico and the USA became public, Fresenius Medical Care established a case-based reporting of cases for all of its dialysis clinics located in Europe, Middle East, Africa and Latin America. This paper aims to describe mortality rates of patients on dialysis and to assess the risk profiles.

**Methods.** The survey was developed in Lotus Notes with a secure browser-based form. The form was open to 602 Fresenius Medical Care clinics located in Europe, Middle East, Africa and Latin America.

**Results.** As of 3 September 2009, 306 cases have been reported by 85 clinics located in Argentina, Chile, Brazil, UK and Spain. The mean age was  $52.7 \pm 17.7$  years. The majority of cases (70.6%) were from 20- to 44-year-old and 45- to 64-year-old subgroups. Moreover, 35.3% had no associated comorbidity, 20.3% had two and 4.6% three comorbidities, with heart disease being the most frequent. Fever was the most common symptom, present in 94.4% of the cases, followed by cough (78.8%) and muscle and joint pain (69.3%). Eighty-seven percent were treated with antiviral agents, the majority with oseltamivir. One hundred and three patients (34%) were admitted to hospital because of influenza. Pneumonia was reported for 69 cases, out of which 52 patients belonged to a high-risk group. Mortality rate of all the patients (confirmed, probable and suspected cases) was around 5%.

**Conclusion.** End-stage renal disease patients should be included in first ranks of the priority list for the influenza A (H1N1)v vaccine, as already advocated by some healthcare authorities.

**Keywords:** dialysis; outcome; pandemic flu; pneumonia

### Introduction

The first two cases of influenza A(H1N1)v were identified in two southern California counties on 15 and 17 April 2009. Since that time cases have been documented throughout the world, initially with most of them occurring not only in the United States but also in Mexico, where influenza A(H1N1)v was later proved to have originated in March 2009. The World Health Organization declared a pandemic on 11 June 2009. On the basis of the surveillance measures put in place by several Healthcare Authorities, the first wave of the pandemic is now ending in many countries, with a progressive decrease in the number of new cases reported [1]. Accurate statistics are not available, but it can be assumed that the first wave of influenza affected a low proportion of the population of the countries involved. History suggests that a second, larger wave of flu is to be expected; however, the timing and severity of a second wave

are completely unknown and may partially depend on the measures put in place by the Healthcare authorities such as containment and vaccination.

The hospitalization rate was estimated to be from 5 to 7% [2–4] of infected people. Previously healthy people without underlying chronic conditions recovered with an uncomplicated hospital course after a median length of stay of 2.5 days (range: 1–7). However, severe cases of novel influenza A(H1N1)v virus infection have included rapidly progressive lower respiratory tract disease resulting in respiratory failure, development of acute respiratory distress syndrome (ARDS) and prolonged intensive care unit admission [5]. The proportion of infected people requiring admission to intensive care units is estimated around 0.6% [4], that is 10% of the hospitalized patients. Mortality rate in the general population has been estimated in the range of 0.2–0.5%.

To date, there are few data on risk factors to predict severe cases and deaths associated with this pandemic. The presence of metabolic conditions (such as diabetes and obesity), respiratory diseases, heart disease, other infections, immunodepression as well as kidney and liver disease has been shown to be associated with higher mortality [6]. In addition, pregnant women might be at increased risk for complication from pandemic H1N1 virus infection [7].

Fresenius Medical Care, treating patients in a large geographical area, can assimilate information from the initially affected countries and transfer the knowledge gained to the countries that expect to face the challenge later on. A population of about 50 000 patients gives FME the unique position of being able to quickly sum up the number of cases and to address important questions such as prognosis and therapeutic options.

After the first cases of influenza A(H1N1)v in Mexico and the United States became public, Fresenius Medical Care established a case-based reporting mechanism for all cases of influenza A from all of its dialysis clinics located in Europe, Middle East, Africa and Latin America. This paper aims to describe mortality rates of a specific population (patients on dialysis), and to assess the risk profiles linked with demographics and comorbidity patterns.

## Methods

The survey was developed in Lotus Notes for easy maintenance and quick overview of reported incidents. A secure browser-based form was made available for feedback. The form was open to all clinics managed by Fresenius Medical Care and located in Europe, Middle East, South Africa and Latin America. Table 1 provides the number of clinics and patients per country as of 30 June 2009.

Prerequisite for the creation of the Pandemic Portal was the pre-existing Contacts Database of all the clinics and the establishment of Clinic Contacts with all the required centre information. Passwords and login credentials have been provided automatically and sent to all clinics via mail.

The Questionnaire included questions related to patient demographics, medical history, data relating to the specific influenza A(H1N1)v infection (date of symptoms' onset, symptom description, availability of laboratory confirmation), information on prophylaxis and therapeutic measures and finally outcome. In the event of missing or conflicting information, the reporter was contacted by the study secretariat and asked to clarify the problematic record.

### Statistical analysis

Quantitative variables were reported as mean and SD, or median and range, depending on the distribution. Absolute and relative frequencies

**Table 1.** Number of dialysis clinics by country covered by the survey (a total of 30 288 patients on treatment in Europe/Middle East, 815 in Africa and 20 262 in Latin America as of 30 June 2009)

Country	Clinics
Argentina	85
Brazil	30
Chile	6
Colombia	37
Croatia	1
Czech Republic	18
Estonia	10
France	34
Germany	8
Great Britain	47
Hungary	24
Ireland	2
Italy	32
Namibia	1
Poland	36
Portugal	34
Romania	8
Russia	3
Serbia	4
Slovakia	18
Slovenia	4
South Africa	26
Spain	60
Sweden	1
Turkey	49
Venezuela	24
Total	602

were used for categorical variables. The impact of clinical characteristics on the outcomes was tested by univariate analysis using  $\chi^2$  or ANOVA, as appropriate. The following variables were taken into account: demographics (age and gender), comorbidity and anti-viral therapy. Logistic regression was used to assess the predictive value of each variable on binary outcomes taking into account the interaction or confounding effect of the other covariates. Relative risk and 90% confidence intervals are reported. Associations with different binary outcomes were tested: development of pneumonia during the clinical course, admission to hospital and death. Analyses were performed using the SPSS version 17.0 (SPSS Inc. Chicago, IL, USA) package.

## Results

As of 3 September 2009, 306 cases of influenza A(H1N1)v have been reported by 85 Fresenius Medical Care clinics located in Argentina (centres: 62, patients: 254), Chile (centres: 3, patients: 16), Brazil (centres: 4, patients: 15), United Kingdom (centres: 12, patients: 17), Spain (centres: 4, patients: 4). This figure corresponds to 3.40% of the patients treated in these 85 clinics.

The date of symptoms' onset of the first case, detected in Argentina, was 1 June 2009. The person was a male of 66 years with diabetes mellitus (ICD-10: E10-E14) and heart disease (ICD-10: I20-I52), on haemodialysis since November 2007. He was treated for 7 days with Oseltamivir 30 mg post-dialysis according to the indications published by Robson *et al.* [8]. He recovered and resumed his usual dialysis treatment in his usual clinic. Until the second half of June, only sporadic cases were reported with all of them occurring in Argentina or Chile. In June, the number of new cases rose to ~50 cases per week. From the end of

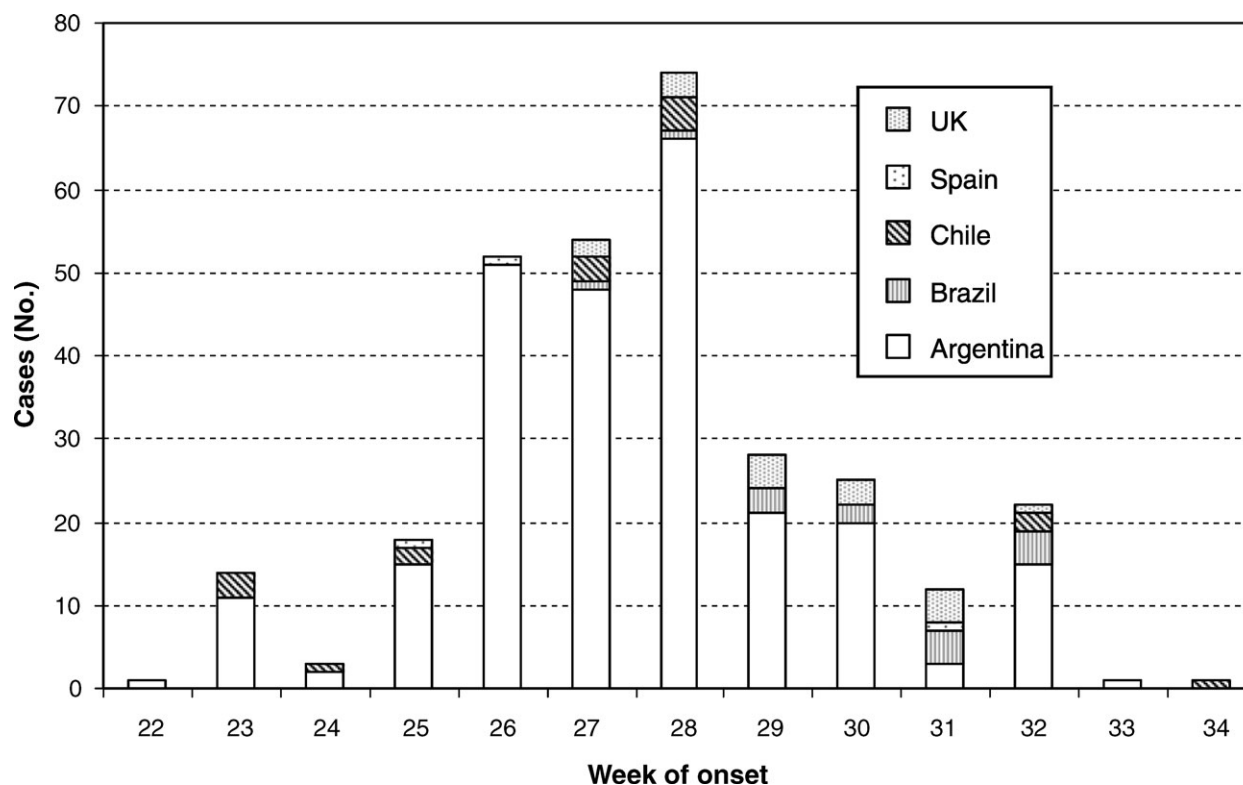


Fig. 1. Incidence of new cases by country and week of onset.

June to mid-July a considerable increase in cases (Figure 1) was seen with a peak of up to 75 cases per week, progressively involving patients treated in Spain (first case: 18 June 2009), Brazil (7 July 2009) and UK (8 July 2009). Since then, the number of new cases per week has decreased. The last case was reported on 28 August 2009.

From the 306 cases among the ESRD patients treated in the FME clinics, 52.5% were male. The mean age was 52.7 years (SD: 17.7). The majority of cases (70.6%) were from 20 to 44 and 45 to 64 years old subgroups. A total of 2.3% of the cases were younger than 20 years, 29.0% were between 20 and 44 years old, 41.6% were between 45 and 64 years old, 16.2% were between 65 and 75 years old and 10.9% of the reported cases were 75 years old or older.

Looking at the proportion of cases in centres with at least one case (Figure 2), below 45-year-old subgroup was most affected with about 4.8% of the patients infected, followed by the 45 to 64 year olds (about 3.7%). In the subgroup 65 years old and >2.3, 2.4% became infected.

Data were also collected on underlying health conditions and risk factors. A third of the patients (35.3%) had no associated comorbid conditions, whilst 20.3% had two and 4.6% three comorbid conditions. The most frequent comorbidity was heart disease (as qualified by an ICD-10: I20-I52), followed by diabetes (ICD-10: E10-E14) and lower respiratory disease (ICD-10: J40-J47). The results are presented in Table 2.

Symptoms were reported for all cases. Fever was the most common symptom, present in 94.4% of the cases, followed by cough (78.8%) and muscle and joint pain (69.3%).

The case definition was performed according to the CDC guidance document [9]: the definition of suspected cases, defined as a person with acute febrile respiratory illness with onset in a community where there are one or more confirmed swine influenza cases, was applicable for about 60% of the patients, 35% were probable cases (checked with a quick test for influenza A) and about 5% were confirmed cases after real-time PCR test. A total of 93.1% of the patients were then treated on haemodialysis in full (70.4%) or partial isolation (22.7%). As a result, during the first wave of the pandemic, patient to patient transmission occurred on one occasion in 37.6% (32 clinics) of clinics, less than four occasions in 62.4% of clinics (53 clinics) and in seven or more occasions in 15.3% of clinics (13 clinics).

About 87% of all the patients (confirmed, probable and suspected cases) were treated, the majority of them with Oseltamivir. Only 2.3% received Zanamivir. A total of 65% of the patients started the therapy within 24 h of onset of symptoms, 28% between 24 and 48 h and only a few cases (7%) started the treatment after 48 h from the onset of the symptoms.

A total of 103 patients (34%) were admitted to a hospital because of influenza. The influenza hospitalization rate was 38%, 13%, 0%, 75% and 12% in Argentina, Brazil, Chile, Spain and UK, respectively. The median hospitalization length was 6 days (range 1–27). We also looked for cases with information on their risk factors and their hospitalization status. The proportion of patients with chronic lower respiratory disease (ICD-10: J40-J47) who were hospitalized for influenza was 52.6%, while the proportion

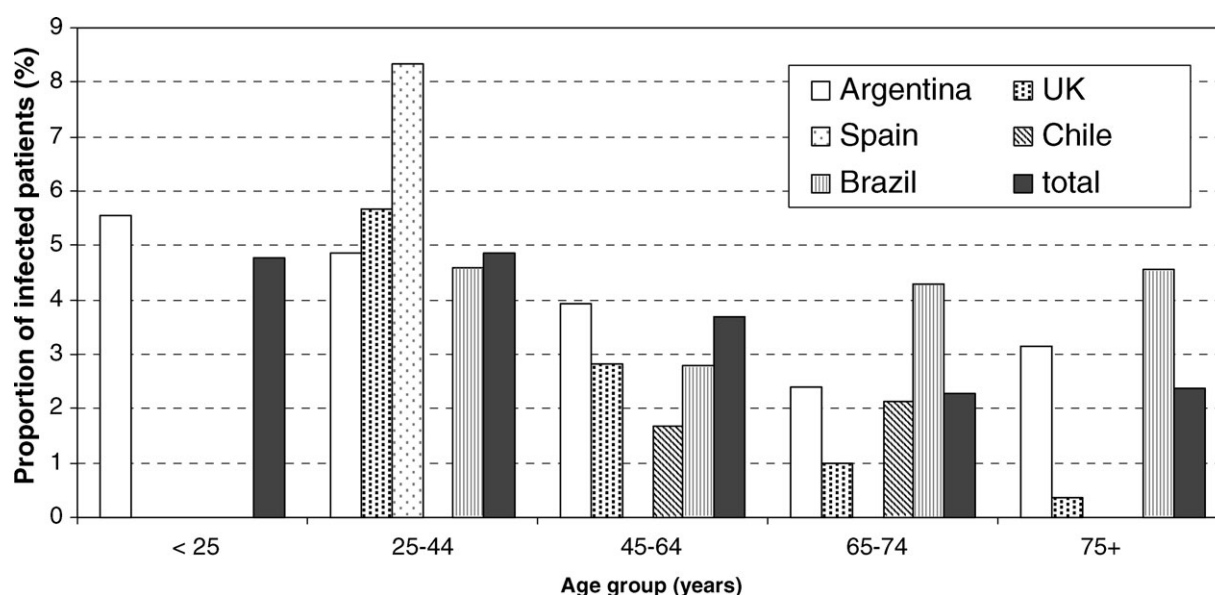


Fig. 2. Proportion of cumulative cases by age group and by country.

Table 2. Distribution of main comorbid conditions according to ICD-10 definition

Disease	ICD-10 code	Proportion of affected patients (%)
Disease of the liver	K70–K77	5.6
Heart disease	I20–I52	38.9
Diabetes mellitus	E10–E14	24.8
Chronic lower respiratory disease	J40–J47	12.4
Immunodeficiency	D80–D89	6.9
Haematologic cancer	C81–C96	0.7
Non-haematologic cancer	C00–C80, C97	4.9

of people without that risk factor that were hospitalized for influenza was 31.1% (OR = 2.46; 90% CI: 1.38–4.39,  $P$ -value = 0.010). The median age was 62 years for those patients with chronic lower respiratory disease and 53 years for the others.

Pneumonia was reported for 69 cases (22.5%), out of which 52 patients belonged to a risk group. The presence of chronic lower respiratory disease was associated with a 3-fold increased risk for developing pneumonia (OR: 2.97; 90% CI 1.63–5.40,  $P$ -value = 0.003) and 46 patients with pneumonia were hospitalized.

Mortality rate of all the patients (confirmed, probable and suspected cases) was around 5%. A total of 53.3% of the deaths were associated with pneumonia. Diabetes (significant) and chronic heart disease (borderline) were associated with a 3-fold increased risk for death (OR: 3.15, 90% CI 1.27–7.79,  $P$ -value = 0.037 and OR: 2.73, 90% CI 1.06–7.05,  $P$ -value = 0.081, respectively).

## Discussion

The analysis of the occurrence of cases as detected by this survey showed that over 90% of them were distributed over an 8-week period with a peak-like pattern. This observation is similar to that reported by other studies on general populations [10], confirming the robustness of the estimations

done on ESRD patients. Most of the cases (83%) were detected in Argentina, which accounts for around 36% of the patients, treated by FME in Argentina, Brazil, Chile, Spain and the UK combined. Clearly, the number of cases in Argentina, when compared with the other countries, was out of proportion to the number of ESRD patients treated. It is possible that the actual incidence in the general population of Argentina was higher than in the other countries, or that the dialysis patients were preferentially susceptible. In support of the first hypothesis we can mention that around 15% of the fatal cases reported worldwide are from Argentina [11], being the third country after the USA and Brazil in the WHO ranking. However, the susceptibility to infection may have been greater as almost all the centres with seven or more cases were located in Argentina. The cumulative number of cases by age group shows that there is a peak in the age groups <45 years and a very low incidence in patients >65 years of age, consistent with other investigations [12–15]. It can be speculated that younger patients are more likely to have a more active life with a higher number of social contacts. It is also possible that the lower frequency of infections in older people may be due to a partial immunity from former infections with H1N1 influenza viruses [16] but may also be due to lack of exposure. We believe that the lower infection rate observed by this study supports the presence of at least a partial immunological protection, since older and younger patients spend

several hours, three times a week, in close contact with each other.

On the onset of the infectious disease, ESRD patients mainly presented with fever, cough, muscle and joint pain. The sequence confirmed what has already been documented in the general population [1]. The lack of specificity of the symptoms together with the complexity and cost of the formal testing (to be performed in highly specialized labs [17]) for confirmation of cases makes the diagnostic process extremely challenging. In addition, in order to be effective and reduce the risk for morbidity and mortality, anti-viral therapy has to be initiated in the very early phases. However, during a pandemic it is very likely that patients presenting with similar symptomatology are likely to be affected by the same disease as the confirmed cases already present in the community. This pragmatic approach was adopted during the pandemic peak by the Argentine and British National Health Service (NHS) healthcare authorities. NHS prepared an algorithm to be used for the prescription of anti-virals, executed by non-professional staff *ad hoc* trained to define and manage 'presumed' and 'suspected' cases [18]. It would appear from this study that other countries may have adopted a similar, although less explicit approach.

In the general population, a hospitalization rate in the range of 6–7% has been estimated. In our experience, it was much higher (38%), even when large variations between countries are taken into account. Admission to hospital results from two factors, the severity of the disease and the availability of beds. Patients with chronic renal disease may have a higher risk for hospitalization as consequence of the comorbid conditions frequently associated with the primary renal disease. This study showed that dialysis patients with chronic respiratory disease, similar to the general population [4,19], had a higher risk for hospital admission. However, in a system of limited resources, hospital admission during a pandemic can become a challenging option. In Argentina, all elective hospital admissions (i.e. for planned surgeries) have been postponed (although this measure was not required in the other countries), leaving as many beds as possible available for managing the pandemic. Under these circumstances hospitalization can be used as a containment measure to limit the spread of the disease in the relatively crowded dialysis centres. Previously hospitalization of infected patients has been openly promoted in some older pandemic management plans, prepared by healthcare authorities, to manage and limit the spread of an avian flu pandemic [20]. However, it has to be stressed that such an approach can work only when the spread of a pandemic in the population is rather limited. In Argentina during the pandemic peak, hospitalization was restricted to compromised patients and measures for isolation at home were implemented. The predicted worst case scenario for the next wave of this pandemic will be an infection rate in the range of 20–30% of the total population over an 8- to 10-week period, the demand on hospital resources, both general and specialized (Intensive Care Unit beds) will be so high as to rapidly overwhelm the available resources. Protective measures such as extensive use of surgical masks and respirators (FFP2 [21] or N95 [22]), strict application of universal precautions, limitation and

control of entries, prompt isolation of suspected cases, etc. have to be implemented in order to limit the spread of the infection in dialysis units. These measures also have the advantage of increasing the confidence of the staff in the safety of the working place. In California, the nurses of the Sutter Solano Hospital filed an urgent plea with the state of California to force their hospital to provide them with proper safety equipment [23]. These measures were promptly applied in the FME network, being already part of the pandemic preparedness plan, put in place for the possible avian flu threat. We believe that the rather limited number of infected staff (only in Argentina: 63 employees, that is 2.7%) is a clear indicator of the level of preparedness of the organization. Accordingly, despite the increased absenteeism due to pregnant women, staff with chronic respiratory diseases, etc. put in force by Argentina authorities, it was possible to maintain the continuity of the activity, ensuring that patients received the life-supporting therapy they required. However, these measures may have worked well during the first wave because of its limited magnitude. In view of this possibility the FME network has adopted a series of escalation measures aimed at maintaining the continuity of the dialysis treatment.

A main reason for hospitalization was the presence of pneumonia. However, little association between symptoms, clinical signs and radiological findings has been reported. CT images showed areas of pulmonary infiltration, often bilateral, in patients with mild initial symptoms followed by rapid evolution to respiratory failure.

Estimating and interpreting case fatality ratios in the general population is difficult, mainly because of inaccurate estimations of both the numerator (number of deaths) and the denominator (number of cases), since many countries have abandoned the systematic laboratory confirmation of all suspected cases. However, to date the case fatality ratio attributable to the current H1N1 pandemic has been estimated at around 0.4% [24].

According to this evaluation, infected patients on chronic dialysis treatment have at least a 10-fold higher mortality in respect to the general population. Actually, Vaillant *et al.* [6] quoted chronic renal failure as a risk factor for mortality. For this reason, the inclusion of chronic renal patients in the groups recommended to receive the novel influenza A(H1N1)v vaccine seems to be fully justified [25,26]. Pneumonia specifically with oxygen saturation at room air <96% was reported to be associated with the majority of the deaths. Few data are available from the current literature. However, according to the experience reported by Kaufman *et al.* [4], severe chest X-ray patterns including mild bi-basal opacities, unilateral lobar consolidation, bilateral/widespread pulmonary infiltrates have been reported. None of the six reported cases showed positive bacterial cultures of blood, urine and tracheal aspirate. Napolitano *et al.* [27] reported on 10 patients admitted to intensive care units. All of them showed abnormal chest radiograph findings with bilateral infiltrates consistent with severe multi-lobar pneumonia or ARDS. Again, none of them had evidence of bacterial infection in blood, bronchoalveolar lavage, or urine cultures. Similar radiological findings and unrevealing blood, urine and sputum cultures were reported by Louie *et al.* [17]. Accordingly, we do not have evidence in favour

of a possible pneumococcal vaccination campaign. As has been reported by Perez-Padilla *et al.* that most of the deaths occurred in Mexico were in patients who required mechanical ventilation [5], a treatment that cannot be considered soft in the case of patients with severe lung involvement. Four of these patients developed ventilator-associated pneumonia, each case with a different cause: *Acinetobacter baumannii*, *Achromobacter xylosoxidans*, methicillin-resistant *Staphylococcus aureus*, or *Escherichia coli*. According to the experience reported by Kaufman *et al.* [4], mechanical ventilation was required for 10–14 days. For this reason, the option to use an artificial lung (extracorporeal membrane oxygenation) has been already applied in New Zealand, Italy and the UK.

In conclusion, pandemic flu is an actual threat we cannot simply ignore. The reported results support the thesis that ESRD patients should be included in first ranks of the priority list for the vaccine, and this has already been adopted by some healthcare authorities. In the meantime, all the players involved in the supply chain of the life-saving dialysis therapy must do whatever is possible to prepare themselves for the next expected wave. Whilst we cannot avoid the external threat, we can do a lot to mitigate the consequences.

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**Conflict of interest statement.** None declared.

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