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Effect of a multimodal strategy for prevention of nosocomial influenza

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UNIVERSITÉ GRENOBLE ALPES
UFR DE MÉDECINE DE GRENOBLE

Année : 2020

**EFFECT OF A MULTIMODAL STRATEGY FOR PREVENTION OF
NOSOCOMIAL INFLUENZA**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Meghann GALLOUCHE

[Données à caractère personnel]

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ABRÉVIATIONS

CHU : Centre Hospitalo-Universitaire

CI : confidence interval

HCW : healthcare worker

HICPAC : Healthcare Infection Control Practices Advisory Committee

IC : intervalle de confiance

ICU : intensive care unit

ILI : influenza-like illness

IQR : interquartile range

IRR : incidence rate ratio

RI : ratio d'incidence

RSV : respiratory syncytial virus

RT-PCR : reverse transcriptase-polymerase chain reaction

USA : United States of America

RÉSUMÉ

Une stratégie multimodale de prévention de la grippe nosocomiale a été mise en place dans notre établissement en 2015-2016. Trois modalités concernaient toutes les unités : promotion de la vaccination pour les professionnels de santé, surveillance épidémiologique et communication. Les unités accueillant un grand nombre de patients grippés ont mis en place 2 autres modalités : amélioration des capacités diagnostiques et port du masque systématique. L'objectif principal était d'évaluer l'efficacité de la stratégie pour diminuer la survenue de la grippe nosocomiale.

Une étude rétrospective portant sur 5 saisons épidémiques (2014-2015 à 2018-2019) et incluant tous les patients adultes hospitalisés avec un test virologique positif pour la grippe a été réalisée au CHU Grenoble Alpes. Le nombre hebdomadaire de cas nosocomiaux de grippe a été analysé par un modèle de Poisson ; des ratios d'incidence (RI) ont été estimés.

Au total, 1555 hospitalisations ont été incluses. Il n'y avait pas de différence significative entre les 5 saisons épidémiques pour les unités ayant mis en place 3 modalités. Dans les unités ayant instauré 5 modalités, il y avait une réduction significative du risque de grippe nosocomiale sur les 3 dernières saisons épidémiques comparées à la saison 2014-2015 (RI=0.39, IC95%=0.19–0.81 en 2016-2017 ; RI=0.49, IC95%=0.24–0.99 en 2017-2018 ; RI=0.48, IC95%=0.23–0.97 en 2018-2019).

L'application de la stratégie à 5 modalités, incluant port de masque systématique et diagnostic rapide, permettrait de réduire de moitié le risque de grippe nosocomiale. Des données médico-économiques sont nécessaires avant d'envisager l'application de ces mesures à plus large échelle.

MOTS CLÉS : grippe, prévention, stratégie multimodale, infections associées aux soins

ABSTRACT

A multimodal strategy to prevent nosocomial influenza was implemented in 2015-2016 in our institution. Three modalities were implemented in all units: promotion of vaccination among healthcare workers, epidemiologic surveillance and communication campaigns. Units receiving a high number of patients with influenza implemented 2 additional modalities: improvement of diagnosis capacities and systematic face mask use. The main objective was to assess the effectiveness of the strategy for reducing the risk of nosocomial influenza.

A retrospective study was conducted over 5 epidemic seasons (2014-2015 to 2018-2019) including all adult patients hospitalized with a positive influenza virological test at Grenoble Alpes University Hospital. The weekly number of nosocomial influenza cases was analyzed by Poisson regression and incidence rate ratios (IRR) were estimated.

A total of 1555 stays were included. There was no significant difference between the 5 influenza epidemic seasons in the units implementing only 3 measures. In the units implementing the 5 measures, there was a significant reduction of nosocomial influenza over the last 3 epidemic seasons compared to the 2014-2015 epidemic season (IRR=0.39, 95%CI=0.19–0.81 in 2016-2017; IRR=0.49, 95%CI=0.24–0.99 in 2017-2018; IRR=0.48, 95%CI=0.23–0.97 in 2018-2019).

Our data mainly suggested that the application of the strategy with 5 modalities, including systematic face mask use and rapid diagnosis, seemed to reduce by half the risk of nosocomial influenza. Further data, including medico-economic studies, are necessary to determine the opportunity of extending these measures at a larger scale.

KEYWORDS: influenza, prevention, multimodal strategy, healthcare-associated infections

INTRODUCTION

The annual burden of influenza in terms of morbidity and mortality, as well as its economic consequences, are well known and have been described repeatedly in the literature [1–5]. Worldwide, estimates indicate that, each year, 5 to 10% of the world's population are affected with seasonal influenza resulting in 290 000 to 650 000 deaths [3]. In France, on average, 2.5 million persons are infected each year. For the 5 last epidemic seasons, the number of emergency stays for influenza-like illness (ILI) ranged from 30 911 in 2014-2015 to 75 500 in 2017-2018 [6–10]. An excess of mortality was registered during the epidemic period, except for the 2015-2016 epidemic season, with 18 300 deaths in 2014-2015, 21 200 deaths in 2016-2017, 12 982 deaths in 2017-2018 and 12 300 deaths in 2018-2019.

The additional influx of patients in emergency departments and hospitalization units generated by seasonal influenza outbreaks can exceed the capacities of care during the peak illness period, as it happened for the first time in our institution during the 2014-2015 epidemic season. Moreover, acquisition of influenza within healthcare facilities is a public health concern given the high proportion of patients at risk of severe influenza in these settings [11,12]. Several nosocomial influenza outbreaks have been described in literature [13–15] and the role of healthcare workers (HCWs) in these outbreaks have been suggested by several studies [16,17].

Although there is limited evidence on vaccination providing a direct protection against influenza for HCWs [18], it has been suggested that there are benefits for the patients with an indirect protection through HCWs' vaccination, especially for patients at risk of severe influenza [19,20]. It could also have a positive impact by reducing the risk of nosocomial influenza [21–23]. Annual vaccination of HCWs is thus generally recommended for all staff in healthcare facilities [24,25]. For patients, the effect of influenza vaccine in protection

against influenza acquisition is also limited with protection ranging from 33 to 67% depending on the subtype [26]. While important, vaccination does not appear sufficient in itself to prevent effectively influenza transmission in healthcare settings. Vaccination should therefore be part of a larger prevention strategy as stated by O'Reilly *et al.* [27]. Other measures have already been discussed in the literature. Face mask use by HCWs appears to be a potential option in order to prevent influenza transmission as well as transmission of other respiratory pathogens. However, its effectiveness remains unclear and acceptability by HCWs may be a concern [28–30]. The use of rapid molecular assays for influenza diagnosis appears also to be an important tool in the management of seasonal influenza outbreaks [31–34]. Indeed, as recommended in national and international guidelines [35,36], when a patient is hospitalized with influenza, control measures must be taken to prevent droplet transmission. Usually patients must be placed in single occupancy rooms and HCWs must wear a surgical mask (droplet precautions). Faster the diagnosis is made, faster these precautions can be implemented, thereby reducing the risk of transmission. Guidelines for management of seasonal influenza in healthcare settings also recommend implementing an active institutional surveillance in order to be able to detect any increased influenza activity and to put in place outbreak control measures if necessary [37,38]. But all these measures can only be applied and effective if they are well understood whether by HCWs, patients or visitors. For that reason, adequate information on influenza should be provided to all these groups. HCWs should receive regular and up-to-date training on healthcare-associated infections, including seasonal influenza.

Review of literature provides a lot of reports on the impact of one or two of these measures. However, the benefit of multimodal strategies has been previously suggested for preventing healthcare-associated infections [39–41]. A multimodal strategy to prevent nosocomial influenza was thus implemented in our institution during the 2015-2016 influenza epidemic

season. Three measures were implemented in the whole institution: promotion of vaccination among HCWs, implementation of an epidemiologic surveillance and communication campaigns. Units receiving a high number of patients with influenza implemented 2 additional measures: improvement of influenza diagnosis capacities and systematic face mask use.

The objective of the present study was therefore to assess the impact of a multimodal prevention strategy on reducing the risk of nosocomial seasonal influenza in a University Hospital over 5 epidemic seasons from 2014 to 2019.

PATIENTS AND METHOD

Patients and settings

Grenoble Alpes University Hospital is a 2133-bed French hospital that recorded over 110 000 emergency stays and 550 000 inpatient days in 2018. A retrospective study was conducted including all patients over 18 years old, who had a positive influenza test in our institution and who were hospitalized between November 2014 and April 2019, during an epidemic period. Pediatric cases, cases occurring outside of influenza epidemic periods (i.e. imported influenza cases during summer) and patients who were not fully hospitalized (emergency stays only, consultations, ambulatory surgery etc.) were excluded. If the acquisition status, nosocomial or community-acquired, was unknown, patients were also excluded. An epidemic period was defined as at least 10 cases per week within the hospital. Five epidemic seasons were considered for this study: 2014-2015 (when epidemic surveillance was not implemented yet), 2015-2016, 2016-2017, 2017-2018 and 2018-2019.

Description of the strategy

A 5-steps multimodal strategy to prevent nosocomial seasonal influenza was implemented in our institution starting during the 2015-2016 epidemic season. Three measures were implemented in all units (n=78): promotion of vaccination among HCWs, implementation of an epidemiologic surveillance and communication campaigns. Two additional measures, improvement of influenza diagnosis capacities and systematic surgical face mask use, were implemented in units which were more susceptible to receive patients with influenza (risk units) only. Risk units included adult emergency department, geriatric units, internal medicine units, infectious diseases unit, post-emergency unit, and pathological pregnancies unit (n=15). Further details on the strategy, including evolution of the measures over the 5 epidemic seasons, are provided in Table 1. The choice of surgical masks (over FFP2 respirator masks) was based on French national recommendations given the absence of superiority of FFP2 respirator masks for respiratory diseases and a greater tolerance with surgical masks [35]. For patients with influenza, the use of FFP2 respirator masks was restricted to invasive procedures such as fibroscopy or respiratory physiotherapy.

The epidemiological surveillance enabled a reinforced management of nosocomial cases and outbreaks. Indeed, when a nosocomial case was identified, contact patients were looked for and they received a prophylactic treatment by Oseltamivir. If more than 2 cases of nosocomial transmission occurred within one unit, several measures were taken to control the cluster: systematic face mask use (if not implemented yet) and prophylactic treatment by Oseltamivir (either to contact patients only or to all patients depending on the risk of severe influenza). These measures were lifted if no new case of transmission was identified in the last 7 days.

Objectives and outcomes

The main objective of our study was to assess the impact of a 5-steps multimodal prevention strategy on reducing the risk of nosocomial seasonal influenza. Secondary objectives were to

evaluate the impact of the strategy on vaccination rates among HCWs and to assess conformity of masks use in designated units. The main outcome of interest was the weekly number of incident nosocomial influenza cases. An incident case was defined as a positive, virological influenza sample associated with symptoms onset occurring at 72h of hospitalization or later [42]. For secondary objectives, outcomes of interest were vaccination rates among HCWs and proportion of adherence to face mask use for HCWs and visitors.

Diagnosis of influenza

Influenza diagnosis tests were performed upon request of physicians on patients presenting fever or feverishness and at least one of the following symptoms: headache, sore throat, cough or myalgia. A sample was taken using a nasopharyngeal swab sample according to the Center for Disease Control and Prevention guidelines [43,44]. A flexible, flocked swab was inserted through the nostril to the nasopharynx, was held in place for 5 seconds and was rotated while being removed. The end of the swab was then placed into the liquid transport media (Sigma Virocult®, MWE, Wiltshire, England) and the applicator stick was cut off. Different types of diagnostic tests for detection of influenza viruses A and B were used:

- RT-PCR R-DiaFlu® (Diagenode Diagnostics, Seraing, Liège, Belgium) capable of detecting influenza viruses A and B. These tests, that have a theoretical turnaround time of 5 hours, were used during all epidemic seasons with 1 panel each day from Monday to Saturday performed in the virology laboratory.
- Rapid RT-PCR GeneXpert® (Cepheid, Sunnyvale, California, USA) capable of detecting influenza viruses A and B as well as respiratory syncytial virus (RSV). These tests, that have a theoretical turnaround time of 35 minutes, were used during all epidemic seasons but their use varied through the study period. They were performed in the virology laboratory. Further details are provided in Table 1.

- Respifinder® 2Smart (multiplex PCR) (Eurogentec, Seraing, Liège, Belgium) capable of detecting a large panel of respiratory pathogens including influenza viruses A and B. These tests were used during all epidemic seasons and their use was restricted to patients hospitalized in intensive care units (ICUs) or on specific demand. They were only performed during weekdays in the virology laboratory and results were available in 4 to 5 days.
- Cobas® Liat System point-of-care tests (Roche Diagnostics, Rotkreuz, Switzerland) capable of detecting influenza viruses A and B as well as RSV. These tests were first assessed over a 2-weeks period during the 2017-2018 epidemic season [45], and were fully available during the 2018-2019 epidemic season. They were performed in the emergency department and results were available in less than 25 minutes.

Data collection

During the 5 epidemic seasons, data were collected prospectively on a daily basis by the members of the infection control unit. All positive influenza tests were retrieved from the laboratory software. Collected data included age, sex and virus type for all epidemic seasons. From the 2015-2016 epidemic season onwards, patient files were systematically checked and collected data also included vaccination status, existence of one or more severity risk factors, Oseltamivir treatment prescription, droplet precautions prescription, ICU stay and death. The status, nosocomial or community-acquired, was determined by an infection control practitioner according to the time of symptoms onset. Data on HCWs' vaccination were provided by the occupational health unit. Global vaccination coverage was available for all epidemic seasons; details on vaccination depending on staff categories and methods were available for the 2017-2018 and 2018-2019 epidemic seasons only. Data on face mask use were obtained by biweekly audits carried out by the staff of infection control unit in the designated units.

Statistical analyses

Epidemics and patients' characteristics were described by numbers and percentages, medians and interquartile ranges (IQR) or means and standard deviations. Groups were compared by means of the Mann-Whitney test, Kruskal–Wallis test, Pearson Chi-squared test or Fisher's exact test as appropriate for continuous and categorical variables.

The weekly number of nosocomial influenza cases was analysed with a parsimonious Poisson regression model adjusting for total number of influenza cases, epidemic season, hospitalization in a risk unit and the interaction terms of the last two variables. Results are presented as incidence rate ratios (IRR) and their confidence interval at 95% (IC95%). Autocorrelation was assessed using an autocorrelation function plot.

All statistical tests were two-tailed and a P value ≤ 0.05 was considered statistically significant. Statistical analysis was performed with Stata 12 software (StataCorp LP, College Station, TX, USA).

Ethics

According to French policy, patient consent was not required since this was a retrospective study and data were declared to the Data Protection Officer of our institution.

RESULTS

Generalities and description of the 5 epidemic periods

A total of 1555 stays with a positive test for influenza were included, they were distributed over the 5 epidemic seasons as follows: 202 in 2014-2015, 152 in 2015-2016, 405 in 2016-

2017, 460 in 2017-2018 and 336 in 2018-2019. The weekly distribution of nosocomial and community-acquired cases for the 5 epidemics seasons are presented in Figure 1.

Epidemic seasons exhibited significant differences in their own features and in patients' characteristics. The profile of influenza epidemic seasons was very variable over the study period, in terms of starting week, duration, and number of cases as shown in Figure 1. In particular, the number of influenza cases hospitalized in our institution increased notably over the last 3 epidemic seasons compared to the 2014-2015 and 2015-2016 seasons. Regarding the case mix (Table 2), median age was significantly different over epidemic seasons ($p=0.0001$) as well as the existence of one or more risk factors of severe influenza ($p<0.0001$). Patients having at least one risk factor for severe influenza had an indication for influenza vaccination. However, patients' vaccination rate did not seem to vary accordingly ($p=0.098$). Type A virus was widely predominant during the 2014-2015, 2016-2017 and 2018-2019 epidemic seasons, whereas during the 2015-2016 and 2017-2018 seasons both type A and type B viruses were circulating with a predominance of type B virus. The proportion of patients receiving antiviral treatment varied significantly over time ($p<0.0001$) as well as mortality that ranged from 3.96% in 2015-2016 to 9.14% in 2016-2017 ($p=0.014$).

A prescription of droplet precautions was found for 66.67% to 78.57% of cases depending of the considered season ($p=0.022$). A possible difference in adherence to droplet precautions between risk units and the others was checked for as it may have influenced the risk of nosocomial influenza. Overall, there was no statistically significant difference in the proportion of droplet precautions prescriptions between risk units and others (72.25% *versus* 70.85%, $p=0.572$). However, mean time between diagnosis (sample date) and droplet precautions prescription was significantly lower in risk units: 0.42 days (+/- 1.27) versus 0.66 days (+/-1.56) in other units ($p=0.0018$).

Despite the measures taken, several units had clusters (> 2 cases) of nosocomial influenza transmission each season: 3 clusters in 2015-2016 (none of them occurring in risk units), 5 clusters in 2016-2017 (including 1 in a risk unit), 1 cluster in 2017-2018 (in a risk unit) and 8 clusters in 2018-2019 (including 3 in risk units). Most of the time, one or more HCWs with ILI were also identified in the corresponding units.

Impact of the strategy on nosocomial influenza

In bivariate analysis, as shown in Table 2, there was no significant reduction of overall number of nosocomial influenza cases over the 5 epidemic seasons ($p=0.086$). Comparing proportions of nosocomial cases among hospitalized patients with influenza between risk units and other units for each epidemic season showed that this proportion was systematically lower in risk units when the multimodal strategy was implemented: 15.96% versus 36.21% ($p=0.004$) in 2015-2016, 14.56% versus 30.15% ($p<0.0001$) in 2016-2017, 13.62% versus 25.41% ($p=0.001$) in 2017-2018 and 18.99% versus 35.03% ($p=0.001$) in 2018-2019. During the 2014-2015 epidemic season (reference), when the strategy was not implemented yet, this proportion was not significantly different between risk units and other units (23.53% and 24.10%, respectively; $p=0.926$).

In Poisson regression adjusting for total number of influenza cases per week, hospitalization in a risk unit, epidemic season and the interaction between these last 2 variables, we found similar results. Being hospitalized in a risk unit prior to intervention (2014-2015 epidemic season) was not significantly associated with an increase or decrease in the occurrence of nosocomial influenza (IRR=1.13, 95%CI=0.64–2.00) as shown in Table 3. There was also no statistically significant association between epidemic season and the occurrence of nosocomial influenza in units implementing 3 measures only. In units implementing 5 measures however, there was a significant reduction in nosocomial influenza occurrence over

the last 3 epidemic seasons compared to the 2014-2015 epidemic season (IRR=0.39, 95%CI=0.19–0.81 in 2016-2017; IRR=0.49, 95%CI=0.24–0.99 in 2017-2018; IRR=0.48, 95%CI=0.23–0.97 in 2018-2019). In 2015-2016, there was also a reduction in nosocomial influenza occurrence in risk units, but this difference was not statistically significant (IRR=0.56, 95%CI=0.23–1.34). The total number of cases was used for adjustment postulating that more patients are hospitalized with influenza more the risk for nosocomial influenza is high, and this variable was actually associated with a higher risk of nosocomial influenza (IRR=1.06, 95%CI=1.06–1.07, for each supplementary case of influenza). Level of autocorrelation was moderate and was considered acceptable.

HCWs vaccination

Global vaccination rates among HCWs has increased from 18.31% for the 2014-2015 epidemic season to 34.70% for the 2018-2019 epidemic season, with rates at 21.96% in 2015-2016, 22.80% in 2016-2017 and 29.10% in 2017-2018. Details on vaccination depending on HCWs categories are provided in Figure 2. Paramedical students represented the category with the highest vaccination proportion (85% in 2017-2018 and 78% in 2018-2019), followed by medical/pharmacy students (74% in 2017-2018 and 57% in 2018-2019), midwives (52% in 2017-2018 and 59% in 2018-2019) and doctors/pharmacists/biologists (42% in 2017-2018 and 45% in 2018-2019). Delocalized vaccination proportion was particularly high for midwives with 41% (out of 52%) in 2017-2018 and 31% (out of 59%) in 2018-2019.

Face mask use compliance

Data on compliance with face mask use by HCWs and visitors were collected through biweekly audits in units implementing this measure and global rates of conformity for each influenza epidemic season are presented in Figure 3. A total of 12997 observations were made on HCWs (2969 in 2015-2016, 2461 in 2016-2017, 3995 in 2017-2018 and 3572 in 2018-

2019) and 3791 on visitors (1145 in 2015-2016, 489 in 2016-2017, 1479 in 2017-2018 and 678 in 2018-2019). Proportion of adequate use for HCWs was high (more than 80%, except for the first season of implementation) and this proportion seemed to have increased throughout the study period from 73.6% in 2015-2016 to 85.7% in 2018-2019. Even though rates were lower overall, the proportion of adequate use for visitors seemed to have increased as well from 45.8% in 2015-2016 to 65.9% in 2018-2019.

DISCUSSION

The strategy with 5 modalities, including systematic face mask use and improvement of diagnosis capacities, seemed to be effective for reducing the risk of nosocomial influenza in our institution. Indeed, in units implementing these measures, the risk of nosocomial influenza was reduced by half over the last 3 epidemic seasons (IRR=0.39, 95%CI=0.19–0.81 in 2016-2017; IRR=0.49, 95%CI=0.24–0.99 in 2017-2018; IRR=0.48, 95%CI=0.23–0.97 in 2018-2019, compared to the 2014-2015 epidemic season). In units implementing only 3 measures however, there was no significant difference in IRRs over the 5 epidemic seasons. The absence of difference between the 2 types of units in 2014-2015 (IRR=1.13, 95%CI=0.64–2.00), when the strategy was not implemented yet, suggests that they were initially comparable for the risk of nosocomial influenza and that the observed differences over the other epidemic seasons can be reasonably related to the application of different strategies.

The application of the strategy with 3 modalities did not seem to be effective to reduce the risk of nosocomial influenza in our cohort. However, no conclusion can be drawn on the actual effectiveness of this strategy given the high number of variations between epidemic seasons that cannot be adjusted on. The epidemic curves presented in Figure 1 showed notable variations in epidemics dynamic and, regarding collected variables, outbreaks exhibited

significant differences in patients' age, influenza types and vaccination rates for high risk patients. The adherence to droplet precautions also varied significantly across seasons ($p=0.022$). Even though the overall proportion of droplet precautions prescriptions was not different, we noticed that the time between diagnosis and prescription was longer in these units (compared to units implementing 5 modalities) and could explain some variations in the risk of nosocomial influenza. It is also important to note that, over the study period, the institutional policy regarding droplet precautions has changed from the 2017-2018 epidemic season. To face the lack of single occupancy rooms, patients with influenza can now be hospitalized in double occupancy rooms provided that a screen is deployed between the beds, the neighbour is immunocompetent and receives a prophylactic treatment by Oseltamivir. This strategy was closely monitored during the 2017-2018 epidemic season and was not associated with a higher risk of nosocomial influenza in neighbours (data not shown).

As described before, the 2 measures differentiating the units were systematic surgical face mask use for HCWs and improvement of diagnosis capacities with rapid tests. Systematic face mask use seemed to be well accepted by HCWs within our institution as shows the increase in adherence to this measure over the study period. Although there is limited evidence on the protective role of surgical face masks against influenza acquisition [28,29], bin-Reza *et al.* suggested that these results could be improved by consistent and correct use of face masks and that this measure should be part of a larger package with a particular focus on hand hygiene [29]. In addition, it was demonstrated that using a surgical mask was associated with reduced aerosol virus shedding [46] which supports the necessity of face mask use by symptomatic individuals, and a study by Ambrosch *et al.* found that systematic surgical face mask use for HCWs was associated with a reduction in the risk of nosocomial influenza [31]. Regarding rapid diagnostic tests, the role of this measure in reducing the risk of nosocomial influenza could be explained by a shorter time to diagnosis resulting in shorter time to

adequate precautions. Several publications have underlined the importance of rapid tests whether for the management or the prevention of nosocomial influenza [31–34]. This measure is also beneficial as it may lead to lower antibiotic consumption [47–49].

A substantial improvement in HCWs' vaccination coverage, that almost doubled, was observed over the study period. The implementation of delocalized vaccination in units by designated nurses seemed to be really effective, particularly for some professional categories such as midwives. This is consistent with literature as several reviews have underlined the importance of improving accessibility to vaccination in order to increase vaccination coverage [50,51]. Another review by Corace *et al.* suggested that psychological theories of behavior change might also be interesting tools in order to increase HCWs vaccination uptake [52]. In line with this, 2 studies were carried out in our institution (a survey on vaccine hesitation in 2017-2018 and an interventional study with implementation intention in 2018-2019) that may have a positive impact in the long term. Despite these encouraging results, vaccination coverage remains insufficient regarding the 75% target set by the European Commission and the 60% target set by the Healthcare Infection Control Practices Advisory Committee (HICPAC) [24]. Similar findings have been reported in other European countries and raise the question of a possible mandatory policy [53]. In a review on mandatory influenza vaccination among HCWs, Pitts *et al.* found that vaccination rates increased over 94% [54].

Despite the measures taken, particularly in units implementing the strategy with 5 modalities, it was not sufficient to completely prevent the occurrence of nosocomial cases and clusters. Given the high number of variables that we cannot control (patients' and visitors' behavior for example), it is likely that the number of nosocomial cases cannot be reduced to zero. However, an important parameter to allow these measures to be fully effective is adherence, and for adherence to be high HCWs must understand the rationale behind the measures. Therefore, communication may be the strongest tool for preventing nosocomial influenza as

stated by Brandt *et al.* [55]. Even though the direct impact of education on the risk of healthcare-associated infections was not demonstrated [56], the information need of HCWs must be assessed [55,57] and regular, up-to-date and adequate training must be provided to HCWs.

To our knowledge, this is the first study in the literature, with over 1500 patients included, to assess the effectiveness of a global prevention strategy against nosocomial influenza unlike many publications that report the evaluation of one or 2 measures only. Our findings suggested a positive impact on both HCWs awareness (which is reflected in the increase of vaccination coverage and adherence towards face masks use) and the risk of nosocomial influenza. A large database was constituted from the start of the reinforced surveillance in 2015-2016 and the continuation of the surveillance for the next epidemic seasons will allow an assessment of the strategy effectiveness in the long run.

Our study had also some limitations. First, as data were not collected for research purposes, it was not homogeneous over all epidemic seasons, especially for the 2014-2015 epidemic season (before implementing the surveillance) that was used as reference. There could have been overlaps for nosocomial cases between the 2 groups (risk units and others) but we postulated that this would be balanced between the 2 groups. Second, we could not determine incidence rates for nosocomial influenza as we did not know the denominator (number of people susceptible to be infected each week). Therefore, we opted for a Poisson regression model. Third, it was not possible to differentiate the units for vaccination coverage, so we cannot exclude that the increase in vaccination was not homogeneous between the 2 groups and that it might have influenced the risk of nosocomial influenza.

As the 5 measures were implemented simultaneously, assessment of the impact of each measure was made difficult. However, the existence of 2 groups allowed us to suspect the

positive role of the 2 measures differentiating the groups: systematic face mask use and accessibility to rapid diagnosis tests. The question is now to determine whether we should implement the strategy with 5 measures to all the units within our institution. Even though our results support this possibility, these measures have only been assessed in units where the frequency of seasonal influenza is high. It is difficult to extrapolate the effectiveness that the addition of face mask use and rapid tests could have in units where the number of patients hospitalized with influenza is low. Moreover, generalizing this strategy would generate substantial additional costs with an increase in the number of diagnostic tests and masks used as well as energy costs for HCWs. Other strategies, such as face mask use for non-vaccinated HCWs only, have been proposed [58,59] but implementation and control seem very complex. Further studies, particularly medico-economic studies, are therefore necessary to determine the opportunity of extending the full strategy to all the units within our institution.

THÈSE SOUTENUE PAR : Meghann GALLOUCHE

TITRE : EFFECT OF A MULTIMODAL STRATEGY FOR PREVENTION OF NOSOCOMIAL INFLUENZA

CONCLUSION

Seasonal influenza outbreaks have, each year, major consequences with an additional influx of patients in emergency departments and hospitalization units that can exceed the capacities to care. This is what happened in our institution during the 2014-2015 epidemic season. Moreover, given the high proportion of patients at risk of severe influenza, preventing transmission of seasonal influenza in healthcare settings must be a priority. In order to better manage this influx of patients and to prevent nosocomial influenza, a multimodal strategy was implemented from the 2015-2016 epidemic season onwards. Three measures were implemented in the whole institution: promotion of vaccination among healthcare workers (HCWs), implementation of an epidemiologic surveillance and communication campaigns. Units receiving a high number of patients with influenza implemented 2 additional measures: improvement of influenza diagnosis capacities and systematic face mask use. Data from 5 epidemic seasons (2014-2015 to 2018-2019) were analyzed retrospectively. The main objective was to assess the effectiveness of the strategy for reducing the risk of nosocomial influenza. Secondary objectives were to assess the impact of the strategy on vaccination coverage among HCWs and to assess adherence to systematic face mask use in relevant units.

In both bivariate analysis and Poisson regression, there was no difference in nosocomial influenza between units implementing 5 modalities and those implementing 3 modalities during the reference season (2014-2015) suggesting that the 2 groups were initially comparable for the risk of nosocomial influenza. The strategy with 5 modalities, including

improvement of influenza diagnosis capacities and implementation of systematic face mask use, seemed to have an impact on nosocomial influenza. Indeed, there was a significant reduction of nosocomial influenza over the last 3 epidemic seasons in units implementing this strategy. These 5 measures could allow reducing by half the risk of nosocomial influenza (incidence rate ratio ≈ 0.5). Effectiveness of the strategy with 3 modalities was not demonstrated, given that there was no significant difference between the 5 influenza epidemic seasons in units implementing only 3 measures.

Assessment of each measure separately was not possible, but we observed an increase in conformity of face mask use with rates over 80% for HCWs over the last 3 epidemic seasons. The benefits of systematic face mask use extend further than influenza as it prevents the transmission of other respiratory pathogens. The positive impact of increasing diagnosis capacities for reducing the risk of nosocomial influenza could be explained by a shorter time to diagnosis resulting in a shorter time to adequate precautions application.

A substantial increase in vaccination coverage among HCWs, that almost doubled from 2014-2015 to 2018-2019 (18.31% and 34.70%, respectively), was also observed. Delocalized vaccination (with designated nurses vaccinating in each unit) seemed to have a positive impact on vaccination rates, especially for some groups of HCWs such as midwives, and should therefore continue to be implemented for the following epidemic seasons. This coverage remains insufficient in regard to the 75% target set by the European Commission and raises the question of a possible mandatory vaccination policy.

Our data mainly suggested that the application of the strategy with 3 modalities seemed to have no effect on nosocomial influenza while the application of the strategy with 5 modalities, including systematic face mask use and rapid diagnosis, seemed to reduce the risk of nosocomial influenza by half. However, these measures have only been assessed in units

where the frequency of seasonal influenza is high. There is a lack of data on how effective the addition of face mask use and rapid tests could be in units where the number of patients hospitalized with influenza is low. Further data, including medico-economic studies, are necessary and a reflection must be carried out to determine the opportunity of extending the full strategy to all the units within our institution.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 20/3/2020

LE DOYEN ET PRÉSIDENT DE LA THÈSE



Pr. Patrice MORAND



Le Doyen de l'UFR de Médecine

Pr. Patrice MORAND

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Table 1. Description of the 5-steps multimodal strategy for nosocomial influenza prevention at Grenoble Alpes University Hospital

| Measure | Details and evolution | Units | Evaluation |
|--|---|-------------|--|
| Promotion of vaccination among healthcare workers | <ul style="list-style-type: none"> - Communication and information (emails, posters etc.) on vaccination - Vaccination in the occupational health unit during all epidemic seasons - Vaccination in units by a referent nurse was implemented from 2017-2018 onwards - A survey on vaccine hesitation was carried out during the 2017-2018 epidemic season - Delocalized vaccination at the hospital lunchroom was implemented from 2018-2019 onwards - An interventional study with implementation intention was carried out during the 2018-2019 epidemic season | All units | Vaccination rate among HCWs determined with data from the occupational health unit |
| Implementation of an epidemiologic surveillance | <ul style="list-style-type: none"> - Daily surveillance of the number of cases within the hospital - Collect of information for all patients with a positive influenza test - Determination of nosocomial status by an infection control practitioner - Outbreak control measures if > 2 cases with nosocomial transmission within one unit | All units | Conformity rate for adherence to droplet precautions |
| Communication | <ul style="list-style-type: none"> - Communication on influenza and vaccination to HCWs, patients and visitors with posters dispatched within the hospital - Weekly emails on vaccination for HCWs - Feed-back to staff: weekly feedback through the intranet portal during the epidemic period, reports in institutional commissions and in risk units at the end of the epidemic | All units | NA |
| Implementation of systematic facemasks use | <ul style="list-style-type: none"> - Systematic facemasks use in risk units - Implementation for all HCWs regardless of their vaccination status - Implementation for the duration of the epidemic period - Benchmarking (weekly feedback for each unit with comparison to the global results) | Risk units* | Conformity rate for HCWs and visitors determined with biweekly audits in risk units during the epidemic period |
| Improvement of diagnosis capacities | <ul style="list-style-type: none"> - Serial tests with RT-PCR R-DiaFlu® (≈ 5h, performed in the virology laboratory on weekdays and Saturday mornings): used during the 5 epidemic seasons - Rapid tests with RT-PCR GeneXpert® (≈ 35min, performed in the virology laboratory): <ul style="list-style-type: none"> - for emergencies only in 2014-2015 - in routine practice for risk units in 2015-2016 (weekdays and Saturday mornings) - in routine practice for risk units and ICUs and on specific demand with justification by clinician from 2016-2017 onwards (weekdays and Saturday mornings only in 2016-2017 and 2017-2018, extended to nights and weekends in 2018-2019) - Rapid point-of-care tests with Cobas® Liat System (≈ 20-25min, performed in the ED): assessment over a 2-weeks period during the 2017-2018 season; then fully available during the 2018-2019 epidemic season | Risk units* | NA |

*Risk units: adult emergency department, geriatric units, internal medicine units, infectious diseases unit, post-emergency unit, pathological pregnancies unit
Abbreviations: HCW: healthcare worker, NA: not applicable, ICU: intensive care unit, ED: emergency department

Figure 1. Weekly distribution of nosocomial and community-acquired influenza cases over 5 epidemic seasons from 2014 to 2019 at Grenoble Alpes University Hospital

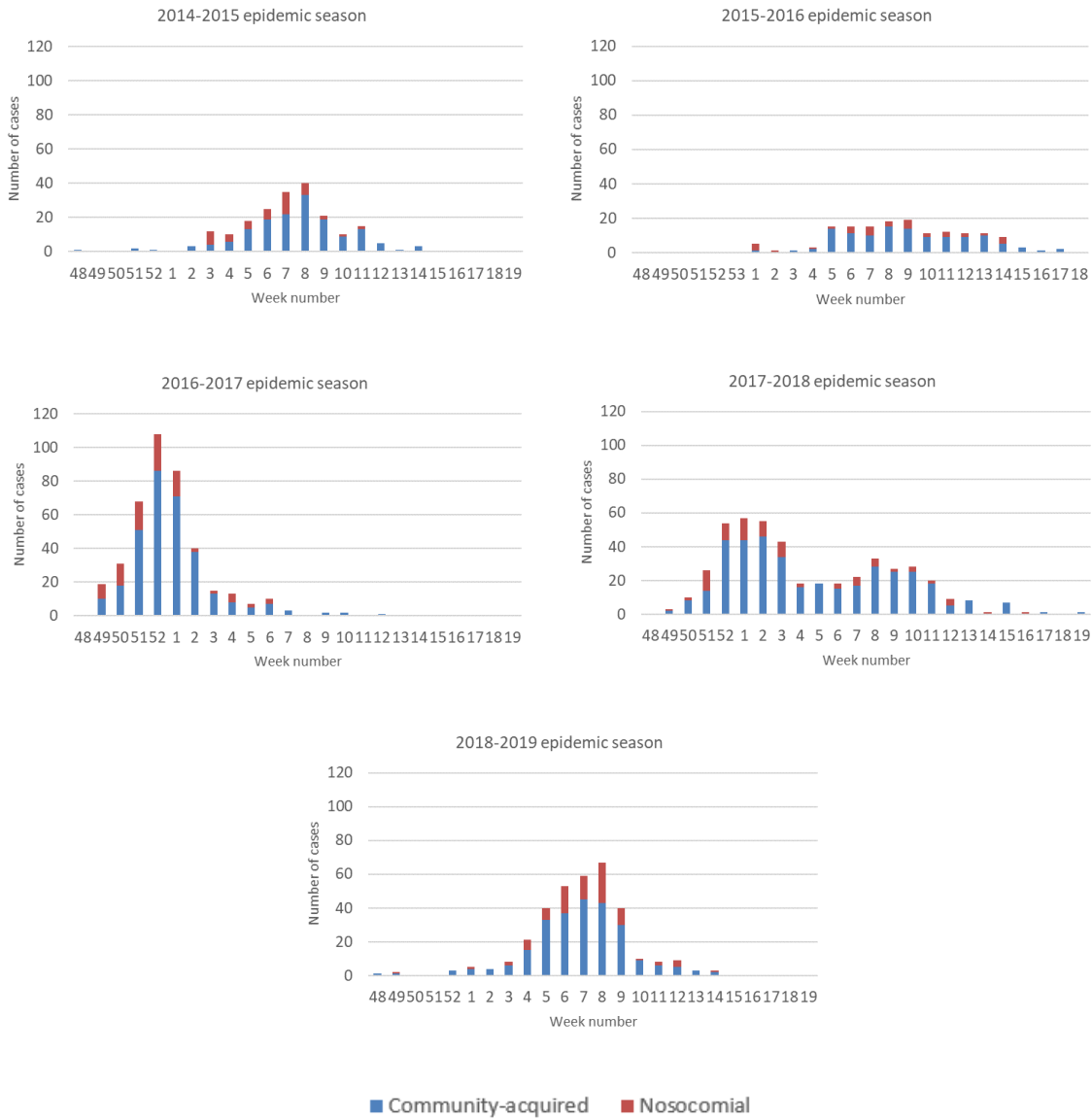


Table 2. Patients' and epidemics characteristics over the 5 influenza epidemics at Grenoble Alpes University Hospital (2014-2019)

| | 2014-2015 N=202 | 2015-2016 N=152 | 2016-2017 N=405 | 2017-2018 N=460 | 2018-2019 N=336 | P value |
|--------------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|--------------------|
| Age, median (IQR) | 79,93 (56.76-87.66) | 71.21 (49.96-81.01) | 81.45 (67.35-87.78) | 78.61 (64.88-87.53) | 79.27 (65.45-86.66) | 0.0001 |
| Male sex, N(%) | 86 (42.57) | 76 (50.00) | 185 (45.68) | 215 (46.74) | 160 (47.62) | 0.683 |
| Virus type | | | | | | |
| - A | 180 (89.11) | 72 (47.37) | 405 (100.00) | 140 (30.43) | 336 (100.00) | |
| - B | 17 (8.42) | 80 (52.63) | 0 (0.00) | 320 (69.57) | 0 (0.00) | - |
| - A/B | 5 (2.48) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | |
| Nosocomial cases, N(%) | 48 (23.76) | 36 (23.68) | 90 (22.22) | 84 (18.26) | 89 (26.49) | 0.086 |
| Severity risk factor(s), N(%) | NA | 118 (78.67) | 388 (95.80) | 420 (91.30) | 324 (96.43) | < 0.0001 |
| Patients vaccination, N(%) | NA | 52 (41.60) | 164 (53.25) | 170 (48.57) | 128 (53.56) | 0.098 |
| Oseltamivir treatment, N(%) | NA | 124 (84.35) | 356 (88.12) | 335 (73.46) | 284 (84.52) | < 0.0001 |
| Droplet precautions, N(%) | NA | 110 (78.57) | 282 (70.15) | 341 (74.45) | 224 (66.67) | 0.022 |
| ICU stay, N(%) | NA | 18 (15.65) | 49 (12.10) | 42 (9.13) | 35 (10.42) | 0.186 |
| Death, N(%) | NA | 4 (3.96) | 37 (9.14) | 32 (6.96) | 12 (6.53) | 0.014 |

Abbreviations: IQR: interquartile range; ICU: intensive care unit

Table 3. Number of nosocomial influenza cases analysed by Poisson regression over 5 epidemic seasons from 2014 to 2019 at Grenoble Alpes University Hospital

| | IRR | 95% Confidence Interval | P value |
|--|------------|--------------------------------|--------------------|
| Risk unit | 1.13 | 0.64 – 2.00 | 0.681 |
| Epidemic season | | | |
| - 2015-2016 | 1.17 | 0.63 – 2.16 | 0.623 |
| - 2016-2017 | 0.97 | 0.55 – 1.68 | 0.903 |
| - 2017-2018 | 1.22 | 0.72 – 2.06 | 0.463 |
| - 2018-2019 | 1.53 | 0.91 – 2.57 | 0.109 |
| Risk unit * epidemic season | | | |
| - Risk unit * 2015-2016 | 0.56 | 0.23 – 1.34 | 0.191 |
| - Risk unit * 2016-2017 | 0.39 | 0.19 – 0.81 | 0.011 |
| - Risk unit * 2017-2018 | 0.49 | 0.24 – 0.99 | 0.050 |
| - Risk unit * 2018-2019 | 0.48 | 0.23 – 0.97 | 0.042 |
| Total number of influenza cases | 1.06 | 1.06 – 1.07 | < 0.0001 |

Abbreviations: IRR: incidence rate ratio

Figure 2. Vaccination rates depending on categories of healthcare workers during the 2017-2018 and 2018-2019 influenza epidemic seasons at Grenoble Alpes University Hospital

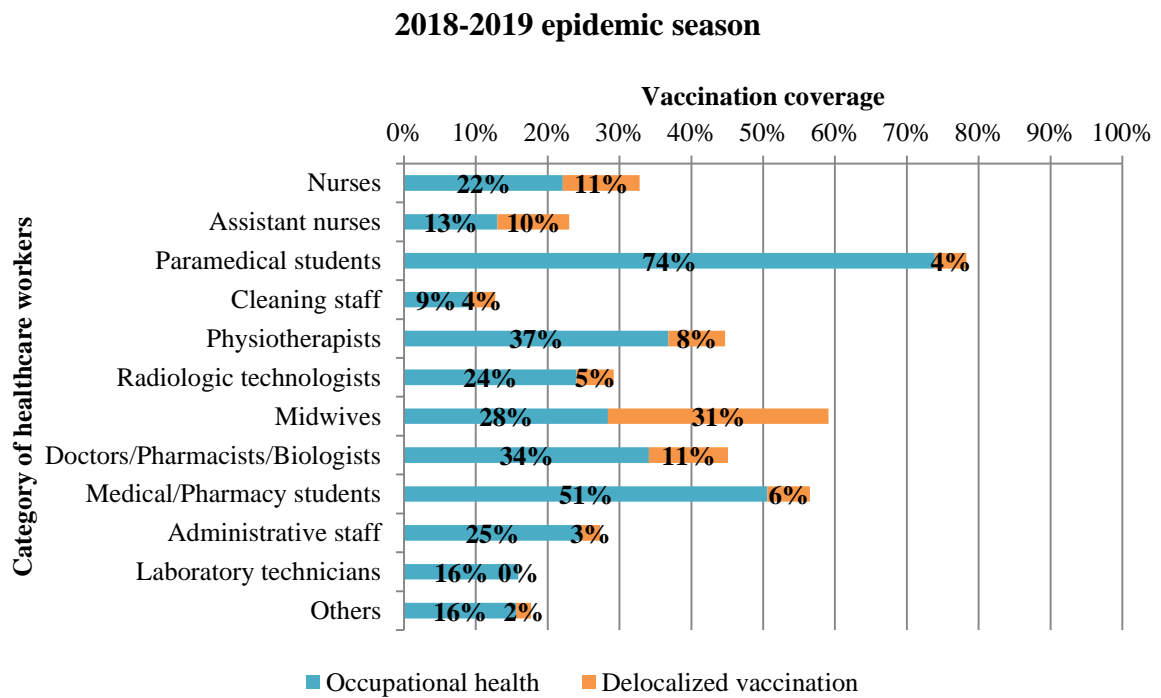
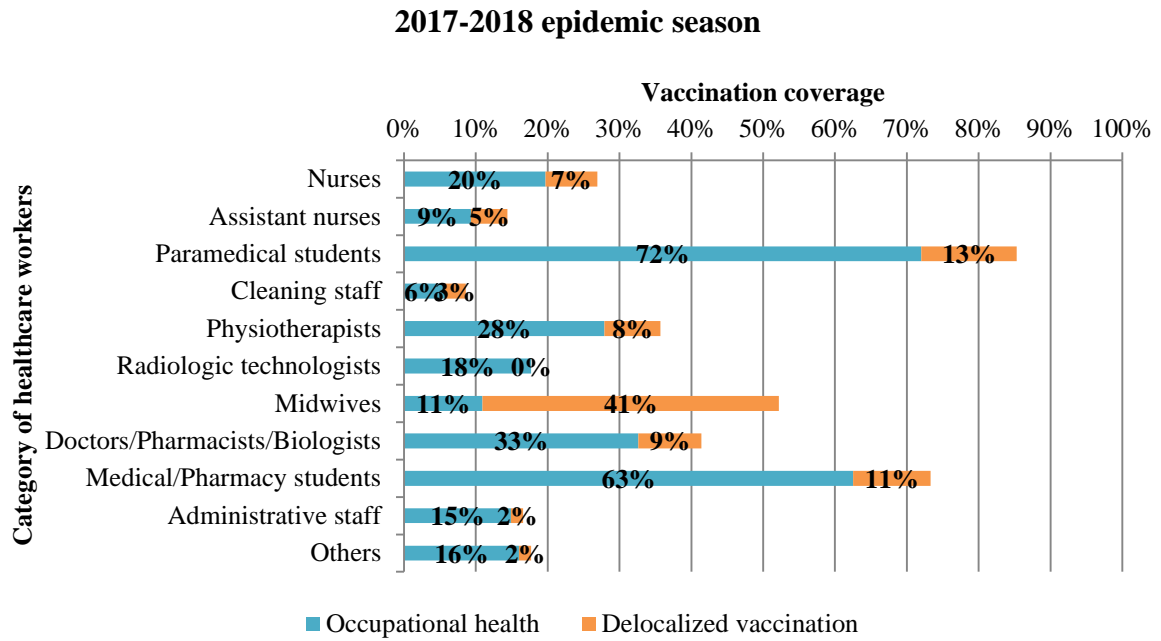
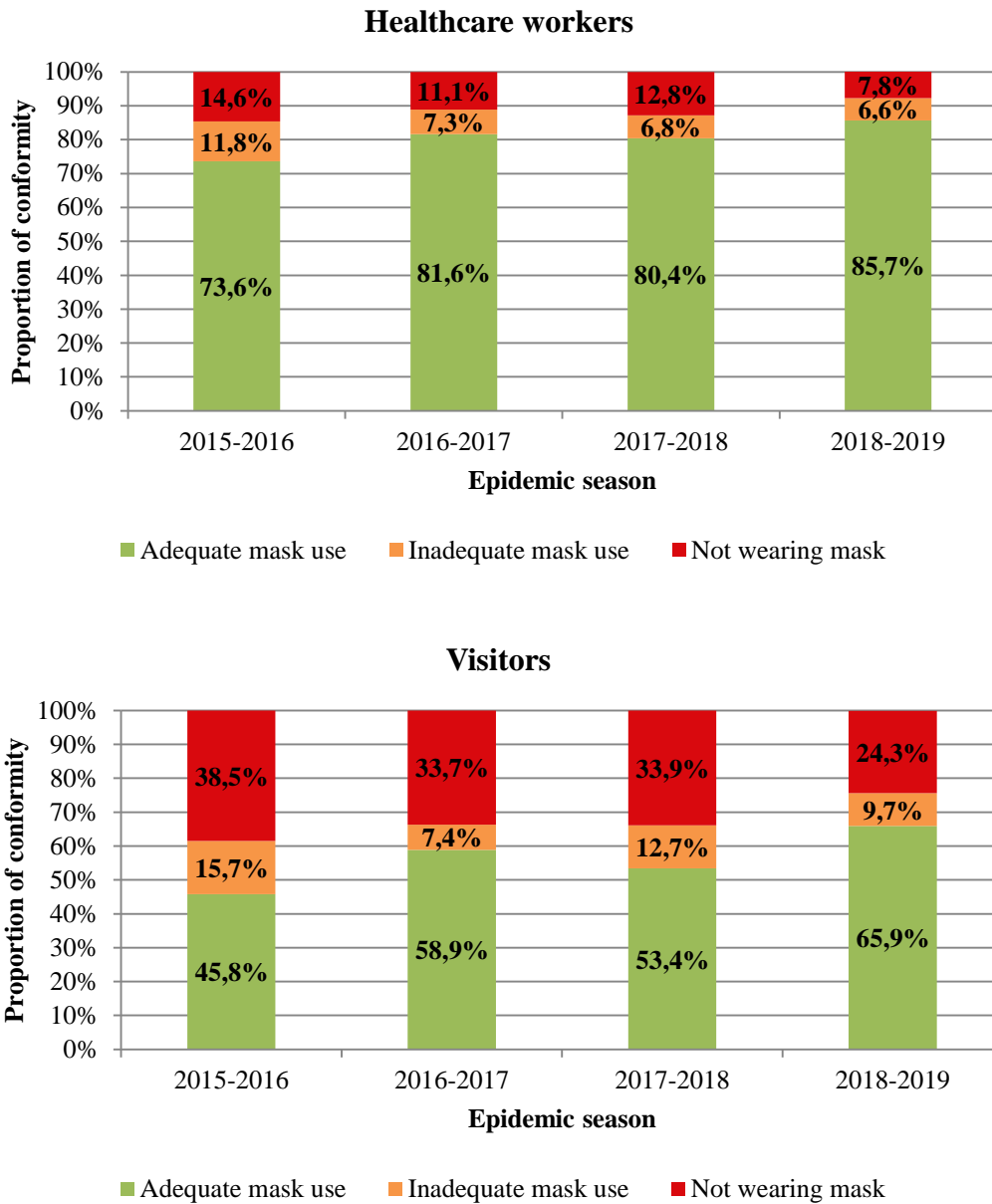
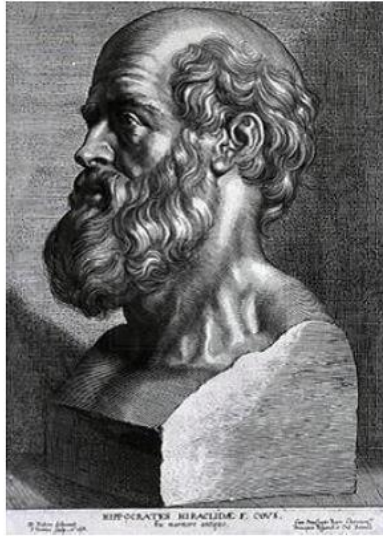


Figure 3. Conformity rates of facemasks use for healthcare workers and visitors over 4 influenza epidemic seasons from 2015 to 2019 at Grenoble Alpes University Hospital





SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.