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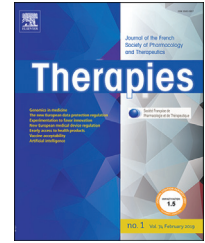


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PHARMACOEPIDEMIOLOGY

Contribution of real-life studies in France during the COVID-19 pandemic and for the national pharmaco-epidemiological surveillance of COVID-19 vaccines

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Summary During the COVID-19 pandemic, EPI-PHARE, a scientific group in pharmaco-epidemiology created by the French National Agency for the Safety of Medicines and Health Products (ANSM) and the French National Health Insurance (Cnam), has reoriented its work program to enlighten health authorities in this health crisis. By exploiting massive and complex data of the French Health Data System (SNDS) from the beginning of the first lockdown in France in March 2020, we were able to publish numerous results on the use, benefits and risks of medicines, on the risk factors of COVID-19 before and after vaccination, and on the benefits and risks of COVID-19 vaccines. Our results were widely taken into account by the French health authorities and allowed them to take informed decision in this pandemic situation in order to ensure the health of the population.

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Abbreviations

ACE	angiotensin-converting enzyme inhibitors
ANSM	French National Agency for the Safety of Medicines and Health Products
ARBs	angiotensin receptor blockers
BNPV	French National Pharmacovigilance Database
CCBs	calcium channel blockers
COVID-19	coronavirus disease 2019
Cnam	French National Health Insurance
EMA	European Medicines Agency
HAS	<i>Hauteautorité de santé</i>
RI	relative incidence
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SNDS	French National Health Data System

Introduction

EPI-PHARE is a scientific group created in 2018 by the French National Agency for the Safety of Medicines and Health Products (ANSM) and the French National Health Insurance (Cnam), with the aim of monitoring the use and benefits-risks of health products in real life conditions and enlightening health authorities in their decision-making process. It has been created after more than 10 years of collaboration between the two pharmaco-epidemiology units of ANSM and Cnam and gathers in a unique place competences in epidemiology, statistics and data-management. EPI-PHARE internally carries out, pilots and coordinates pharmaco-epidemiological studies using complex and massive data from the French Health Data System (SNDS), in order to provide autonomous, independent and responsive public expertise in pharmaco-epidemiology and health security and to enlighten public authorities in their decision-making.

At EPI-PHARE, from the beginning of the health crisis linked to the coronavirus disease 2019 (COVID-19) pandemic and the lockdown measures decided by the President of the French Republic, we reminded our institutional members of our total commitment and full mobilization in the pursuit of our missions in this exceptional period. All EPI-PHARE staff have remained mobilized to carry out their missions and, while ensuring the continuation of its activities, a large part of our work program was reoriented on themes concerning the COVID-19 pandemic. Thus, since the first lockdown of March 2020 in France, EPI-PHARE has mobilized its expertise to quantify and characterize the use and risks of health products concerned by this crisis situation, and provide its expertise towards health authorities.

Use and risks of health products during the COVID-19 pandemic

Monitoring the use of medicines and health products in France

EPI-PHARE monitored the use of medicines of more than 50 therapeutic classes since the first lockdown in France in

March 2020 and over a period of more than 1 year [1–6]. The results after analysis of more than 4 billion prescription lines reimbursed by health insurance for the whole French population showed among others a stock phenomenon of medicines at the beginning of the first lockdown, with a very strong growth in the dispensation of prescription drugs in pharmacies for chronic diseases (drugs for cardiovascular pathologies, diabetes, mental disorders in particular). The results also showed a huge fall in the dispensation of medicines for imaging diagnosis and the fall of mandatory vaccination of children, which lead French authorities to call for the continuation and amplification of mandatory childhood vaccination.

In this large study, we also pointed out the increasing use of anxiolytics, hypnotics and antidepressants with strong increases in dispensation and initiation compared to the expected. Overall, over the more than one-year period since the start of the first lockdown, between March 2020 and April 2021, there were +1.9 million antidepressant, +440,000 antipsychotic, +3.4 million anxiolytic, and +1.4 million hypnotic dispensing compared to expected numbers.

The COVID-19 pandemic also had an impact on routine surgical procedures, we quantified at EPI-PHARE changes in five surgical procedures during this period, namely cataract surgery, hip and knee replacements, coronary revascularization with angioplasty, and definitive cardiac stimulation. From data of the SNDS between January 1, 2019, and June 30, 2021, we identified a total of 2,153,857 hospitalizations for cataract surgery (0.6% revision), 398,213 for hip replacement (10.9% revision and 26.9% emergency), 276,607 for knee replacement (8.2% revision), 471,318 for coronary angioplasty (48.7% emergency), and 178,441 for pacemaker (27.6% revision). In detail, we pointed out a marked decrease for 4 routine surgical procedures compared with expectations until at least the first half of 2021. The activity was lower than expected in 2020 (cataract surgery: –21.9%; hip replacement: –13.4%; knee replacement: –24.6%; coronary angioplasty: –11.2%) with no catch-up in the first half of 2021 (cataract surgery: –5.0%; hip replacement: –9.9%; knee replacement: –22.0%; coronary angioplasty: –12.1%). Revisions and non-elective procedures also decreased, but to a lesser extent. However, cardiac stimulation activity was almost in line with expectations (–2.6% [–4.9; –0.3]/+0.6 [–2.2; +3.4]) [7].

Risks of medicines concerned by the COVID-19 pandemic

EPI-PHARE has realized several studies on the risks of COVID-19 associated with certain drugs; among them we can cite synthetic antimalarials, antihypertensive drugs and aspirin.

In the first months of the pandemic, we conducted a nationwide cohort study using data from SNDS in order to evaluate the risks of hospitalization, oro-tracheal intubation and death during hospital stays for COVID-19 in patients using long-term synthetic antimalarial drugs (AMD: hydroxychloroquine or chloroquine) and to compare them to the risks in the general population. From a total of 54,873 patients with long-term use of synthetic antimalarial drugs matched with 155,689 unexposed individuals, no difference was observed between synthetic AMD long-term exposure

and unexposed group regarding the risk of hospitalization with COVID-19 (HR, 1.15 [0.86; 1.55]). No more difference was observed in subgroup analyses neither regarding the risk of intubation or death during a hospital stay for COVID-19 (aHR, 0.66 [0.29; 1.51]). The results did not suggest any preventive role for long-term use of synthetic antimalarial drugs on the risk of hospitalization, intubation or death for COVID-19, and were added to the corpus of scientific publications that showed no effect of hydroxychloroquine or chloroquine in the care of COVID-19 patients [8].

During the pandemic, low-dose aspirin has been reported as a potential drug candidate to treat or prevent severe COVID-19. We thus realized at EPI-PHARE a pharmaco-epidemiological study in order to investigate whether low-dose aspirin used for primary cardiovascular prevention was associated with a lower risk of severe COVID-19. In a large cohort of 31.1 million patients aged over 40 years without known cardiovascular comorbidities, 1.5 million had reimbursed low-dose aspirin at least 3 times in the 6 months before the pandemic. Hazard ratio in fully adjusted models showed close to null associations between low-dose aspirin and risk of hospitalization (HR, 1.03 [1.00; 1.06]) or death/intubation for COVID-19 (HR, 1.04 [0.98; 1.10]). This study did not show any evidence of an effect of low-dose aspirin used for primary cardiovascular prevention in reducing severe forms of COVID-19 [9].

We also investigated the association between antihypertensive drugs and COVID-19 risks of hospitalization, intubation or death. Indeed, some results suggested negative associations with hypotheses pointing out a positive relationship between use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19. We examined the different COVID-19 risks in patients treated by angiotensin-converting enzyme inhibitors (ACE) and angiotensin receptor blockers (ARBs) compared with calcium channel blockers (CCBs). Using the data from the SNDS, we constructed a cohort of 2 million hypertensive patients followed for 16 weeks in which 2,338 were hospitalized and 526 were intubated or died for COVID-19. Patients treated with ACE inhibitors and ARBs were at lower risk of COVID-19 hospitalization compared with patients treated with CCBs (HR, 0.74 [0.65; 0.83] and 0.84 [0.76; 0.93], respectively) and at lower risk of intubation/death. In addition, patients treated with ACE inhibitors were at slightly lower risk compared to ARB users. These results, who have been awarded by the American Heart Association the prize for the best article on population data published in the journal *Hypertension* in 2021, overturned the initial assumption that patients treated with sartans were at greater risk of severe COVID-19, and have been subsequently confirmed by other studies [10].

Factors associated with the risk of COVID-19

In the pandemic context, fast-track access to hospital medico-administrative databases has been implemented in France, and EPI-PHARE worked in near real-time on the entire French population (67 million people). We were thus able to estimate the chronic diseases and health conditions associated to COVID-19 related hospitalization and in-hospital mortality. In the whole French population

between February 15, 2020 and June 15, 2020, we identified 87,809 people who were hospitalized for COVID-19 and 15,661 people who died in hospital. We confirmed in this study that age is by far the most important risk factor for severe forms of COVID-19, with a risk of hospitalization more than 5-fold higher and a risk of in-hospital mortality more than 100 – fold higher in people aged 85 years and older compared to people aged 40 to 44 years. We also highlighted that almost all chronic conditions are associated with increased risks of hospitalization and in-hospital mortality for COVID-19. In particular, these results showed the extremely high vulnerability of patients with Down syndrome to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus with a 7 times greater risk of hospitalization and 23 times greater risk of death [11,12].

These important results were publicly released shortly after the beginning of the vaccination campaign and led the French authorities to integrate people with Down syndrome in the priority population to be vaccinated against COVID-19. We also showed in a further study that after vaccination, which has dramatically reduced the occurrence of severe forms of COVID-19, a residual risk remains for the elderly, immunocompromised, and polypathological populations [13].

Pharmaco-epidemiological surveillance of COVID-19 vaccines in France

With the beginning of the COVID-19 vaccination campaign, ANSM set up a specific system for a strong surveillance of the efficiency and security of COVID-19 vaccines in France. This system, which is part of the risk management plan coordinated by the European Medicines Agency (EMA), relies on both pharmaco-vigilance, i.e., the analysis of adverse drug reactions reported by healthcare professionals and vaccinated individuals in the national pharmacovigilance database (BNPV) and pharmaco-epidemiology that aims at measuring the efficiency of COVID-19 vaccines and to quantify their risk of adverse drug reactions at the population level.

The objectives of this reinforced surveillance were to perform an ongoing evaluation of the efficiency and safety of COVID-19 vaccines in order to take rapid action if necessary, and to allow the Ministry of Health to adapt the vaccination strategy to ensure the safety of vaccinated individuals. Within the framework of this system, EPI-PHARE has been mandated to carry out pharmaco-epidemiological studies on the entire population targeted by vaccination in France in order to assess both risks and efficiency of vaccines in real-life [14–19].

Risks of COVID-19 vaccines

As vaccination campaign began in France for people aged 75 years or older, pharmaco-vigilance reported signals for severe cardiovascular events for Pfizer-BioNTech vaccine: high blood pressure and cardiovascular, thromboembolic and bleeding disorders. On the basis of these signals, we initiated at EPI-PHARE a pharmaco-epidemiological study in order to evaluate the short-term

risk of hospitalization for myocardial infarction, stroke, and pulmonary embolism after BNT162b2 mRNA (Pfizer-BioNTech) vaccine in people 75 years of age and older. From data of the SNDS, we identified, as of April 30, 2021, nearly 3.9 million persons aged 75 years or older that had received at least 1 dose of the Pfizer-BioNTech vaccine. Three million two hundred thousand (3.2 millions) people aged 75 years or older had received 2 doses. In this study, our results do not support any association between Pfizer-BioNTech's COVID-19 vaccine and the occurrence of serious cardiovascular events within 14 days of vaccination in people aged 75 years or older, regardless of the post-vaccination period considered (from 1 to 14 days after the 1st and 2nd dose) [14,18]. In a second study over 46.5 million adults younger than 75 years in France, we did not highlight any association between the Pfizer-BioNTech or Moderna vaccine and severe cardiovascular events. However, an association was found between the first dose of the Oxford – AstraZeneca vaccine and acute myocardial infarction and pulmonary embolism in the second week after vaccination (relative incidence (RI): 1.29 [1.11; 1.51] and 1.41 [1.13; 1.75], respectively). On the same way, an association was found between the first dose of Janssen and Astra Zeneca vaccines and myocardial infarction in the second week after the injection (RI, 1.75 [1.16; 2.62] and 1.29 [1.11; 1.51] respectively). The first dose of the AstraZeneca COVID-19 vaccine was also associated with a higher risk of pulmonary embolism in the second week after the injection (RI, 1.41 [1.13; 1.75]) [20]. These two studies confirmed the safety of mRNA vaccines against the risk of serious cardiovascular events in adults, and pointed out that adenovirus vaccines appear to be associated with a slight increase in the risk of myocardial infarction and pulmonary embolism in adults within two weeks of injection.

Beside serious cardiovascular events in adults, the pharmaco-vigilance system reported an increased risk of myocarditis and pericarditis with COVID-19 mRNA vaccines, mainly after the second dose in young men [21]. In a period when vaccination campaigns was not yet widely deployed in France, we thus initiated a pharmaco-epidemiological study in order to evaluate the association between COVID-19 mRNA vaccines and the risk of myocarditis and pericarditis in persons aged 12–50 years. In this study, we analyzed 1,612 cases of myocarditis and 1,613 cases of pericarditis that occurred in France between May 12, 2021, and October 31, 2021, which were matched with 16,120 and 16,130 control subjects, respectively. Increased risks of myocarditis and pericarditis were found in the first week after vaccination, and particularly after the second dose (Pfizer-BioNTech vaccine: $OR_{\text{myocarditis}}$, 8.1 [6.7; 9.9]; Moderna vaccine: $OR_{\text{myocarditis}}$, 30 [21;43]). The largest associations were observed for myocarditis following Moderna vaccination in persons aged 18 to 24 years [19]. Following our results, the French *Haute autorité de santé* (HAS), that evaluates health products from a medical and economic perspective and establish best practices recommendations, decided to prioritize Moderna vaccine for people aged 30 years and more.

Efficiency of COVID-19 vaccines

Apart evaluation of the risks after COVID-19 vaccination, we conducted at EPI-PHARE several studies in order to evaluate the efficiency of COVID-19 vaccines [15–17].

In clinical trials, mRNA-based vaccines have shown an efficacy of 92–95% in the prevention of COVID-19 in adults. In a first study, which took place at the beginning of the vaccination campaign in France, we estimated the impact of vaccination on the risk of serious forms of COVID-19 (i.e., with hospitalization) in adults aged 75 or older. In a cohort of 1,422,461 vaccinated subjects matched with two control subjects, adjusted hazard ratio for hospitalization for COVID-19 from the seventh day after the second dose of mRNA vaccine was estimated at 0.14 (HRa=0.14 [0.11; 0.17]), which corresponds to an estimated 86% risk reduction in people aged 75 and older [15].

As the vaccination got widely deployed in France, we then studied the effectiveness of COVID-19 vaccines in adults aged 50 or older. In this study, we included 11,256,832 vaccinated subjects 63.6% ($n=7,161,658$) with the Pfizer-BioNTech (BNT162b2) vaccine, 7.6% ($n=856,599$) with the Moderna (mRNA-1273) vaccine, and 28.8% ($n=3,238,575$) with the AstraZeneca (ChAdOx1) vaccine, and 11,256,832 unvaccinated controls. The vaccine effectiveness after two doses against hospital admission for COVID-19 ranged from 91% to 95% for the three Pfizer-BioNTech, Moderna, and AstraZeneca vaccines. For in-hospital death, the effectiveness after the second dose was 91% and 96% for of Pfizer-BioNTech and Moderna vaccines respectively, and 88% for AstraZeneca vaccine [16].

At last, in a third published study, we examined the effectiveness of Janssen (Ad26.COV2.S) vaccine compared to Pfizer-BioNTech (BNT162b2 mRNA) vaccine. In a cohort of 689,275 Janssen and 689,275 Pfizer-BioNTech vaccinated people, the risk of hospitalization for COVID-19 after vaccination was approximately 5 times higher with Janssen than with Pfizer-BioNTech vaccine. Considering an effectiveness of Pfizer-BioNTech vaccine of 92% (95% CI, 90%–94%), the effectiveness of Janssen vaccine was estimated at 59% (95% CI, 33%–75%), thus supporting the injection of a second dose with a mRNA vaccine in people who received the Janssen vaccine as recommended both in France and in the US [17].

Conclusion

During the COVID-19 pandemic, EPI-PHARE was strongly mobilized to provide its expertise to health authorities and produced numerous results on the use and risks of health products, the risk factors for severe COVID-19 in vaccinated and unvaccinated individuals and on the epidemiological surveillance of COVID-19 vaccines.

Our work has been endorsed by the public authorities and participated to major public health measures: call to continue mandatory childhood vaccination during the epidemic and lockdowns, highlighting of the impact of the epidemic on the mental health of French people, adaptation of the vaccination strategy against COVID-19 towards specific population (inclusion of people with Down syndrome), effectiveness of vaccination against COVID-19 and the major impact of mRNA vaccination on reducing the risk of severe COVID-19, quantification of risks of myocarditis and recommendation not to use Moderna vaccine for people under 30.

In parallel with our scientific production for health authorities, we maintained our transparency policy and have

made all our reports public. Our reports were regularly the subject of press releases in association with ANSM and Cnam, and have been widely distributed by the national, regional and even international press. In addition to this general communication, we published from the beginning of the pandemic in March 2020, 22 articles related to our COVID-19 program in international peer-reviewed journals. This scientific communication had the double objective of having our results evaluated by peers in order to reinforce the scientific credibility of EPI-PHARE and to disseminate our results to the international scientific community in the fight against the COVID-19 pandemic.

The fast response of EPI-PHARE during the COVID-19 pandemic is the result of a long history of collaboration between ANSM and Cnam who understood very early on the advantages of implementing pharmaco-epidemiological studies using medico-administrative databases. It allowed the French authorities to have reliable data on the use, benefits and risks of health products for their decision-making during a health crisis, and highlighted the full potential of the exploitation of medico-administrative databases. The unique model of EPI-PHARE and its results during the COVID-19 pandemic could encourage other health authorities to develop high-level competences in epidemiology, biostatistics and data-management, in order strengthen their decision-making process for the safety of patients.

Disclosure of interest

The authors declare that they have no competing interest.

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