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## ORIGINAL ARTICLE

# Trends in anti-infective use during pregnancy in France between 2010 and 2019: a nationwide population-based study

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**Aims:** To describe the trends in anti-infective use during pregnancy between 2010 and 2019 and determine whether they were prescribed according to drug foetal safety international classification systems.

**Methods:** We conducted a population-based, nationwide study using the French national health data system including all pregnancies ended between 2010 and 2019. Anti-infective agents were considered according to their pharmacological group and potential harmful risk using the Australian and Swedish classification systems. Prevalence rate was estimated annually and by trimester. Average annual percent change (AAPC) and 95% confidence intervals (CIs) were calculated using Joinpoint regression.

**Results:** Among 7 571 035 pregnancies, 3 027 031 (40.0%) received  $\geq 1$  antibacterial. This proportion decreased significantly from 41.5% in 2010 to 36.1% in 2019 (AAPC =  $-1.7\%$ , [95%CI,  $-2.5$  to  $-1.0\%$ ]). Conversely, use of antiviral agents increased during the 10-year study period for anti-herpes simplex virus agents (AAPC =  $4.4\%$ , [3.7–5.2%]), influenza agents (AAPC =  $25.4\%$ , [6.2–48.1%]) and for HIV-antiretroviral agents (AAPC =  $1.3\%$ , [0.6–2.0%]). Use of influenza vaccine increased from 0.2% in 2010 to 4.2% in 2019 (AAPC =  $49.7\%$ , [39.3–60.9%]). Among all pregnancies, 0.9% had been exposed to a potentially harmful anti-infective agent increasing from 0.7% in 2010 to 1.2% in 2019 (AAPC =  $6.4\%$ , [4.4–8.5%]).

**Conclusion:** Based on >7 million pregnancies identified from French nationwide data, this study showed that antibacterials are frequently prescribed during pregnancy although their use has decreased over the past 10 years. Our results suggest that anti-infective agents are generally prescribed in accordance with recommendations, although with a potential for improvement in influenza vaccination.

## KEYWORDS

antibacterials, antifungals, anti-infective agents, antivirals, French national health data system, pregnancy

## 1 | INTRODUCTION

Due to the immunological and physiological changes occurred during pregnancy, pregnant women may be more susceptible to developing certain infections or at an increased risk of complications from infection.<sup>1</sup> Regarding bacterial infections, urinary tract infections and vulvovaginal candidiasis are more common in pregnancy, and, along with upper respiratory tract infections, represent nearly 3/4 of all treated maternal infections. Appropriate treatment of infectious diseases during pregnancy remains an important strategy for protecting maternal and infant health. However, prescribing drugs during pregnancy represents a challenge for the physician driven by the risk-vs.-benefit balance. Infections need to be treated, while protecting the foetus against possible side-effects of the drugs. Safety and efficacy information are not usually available from randomized controlled trials, as pregnancy is often a standard exclusion criterion.

Anti-infective (AI) agents are among the most common drugs prescribed during pregnancy worldwide with around 20–45% of pregnant women exposed to antibacterials.<sup>2–11</sup> While many AI agents are generally considered safe for the foetus, there are concerns that the use of several antibacterials<sup>12–18</sup> or systemic antifungals<sup>19,20</sup> during pregnancy may lead to adverse outcomes including spontaneous abortions or major birth defects. Moreover, exposure to AI agents may also cause the emergence of antimicrobial resistances and alter both mother and infant gut microbiome composition.<sup>21,22</sup>

To guide health care professionals in prescribing drugs during pregnancy, various risk classification systems have been developed to classify drugs into risk group according to their foetal safety: the 2015 US Food and Drug Administration narrative structure for pregnancy and lactation labelling rule,<sup>23</sup> the Australian Drug Evaluation Committee (ADEC)<sup>24</sup> and the Swedish Catalogue of Approved Drugs (FASS).<sup>25</sup> These last 2 classifications consist of 4 or 5 categories (A, B, C, D and X) and several subcategories to categorize the teratogenic potential of drugs. These 2 classification systems are similar except that, in addition to categories A, B1, B2, B3, C and D, the Australian system uses a category X for drugs with the highest risk of causing permanent damage to the fetus.

Several studies have described trends in overall drug prescriptions during pregnancy but only few have considered anti-infective drugs using pharmacological subgroups,<sup>2,3,9</sup> and none with data from the last decade.

The aims of the present study were to describe the trends in anti-infective agents use during pregnancy between 2010 and 2019 and to determine whether they were prescribed according to international classification systems of drug foetal safety in a large-scale, population-based, nationwide study using the French national health data system.

## 2 | METHODS

### 2.1 | Data source

The French national health data system (Système National des Données de Santé, SNDS) covers >99% of the French population (around

### What is already known about this subject

- Anti-infective agents are commonly prescribed during pregnancy worldwide.
- Several studies have described trends in drug prescriptions during pregnancy but only few have considered anti-infective drugs using pharmacological subgroups, and none with data from the last decade.

### What this study adds

- Antibacterials are frequently used during pregnancy, although there has been a downward trend over the last decade.
- Use of antivirals, antifungals and influenza vaccine increased in the past 10 years.
- Anti-infective are generally prescribed in accordance with recommendations, with however a potential for improvement in influenza vaccination.

66 000 000 people). Each person is identified by a unique, anonymous number. The SNDS contains all outpatient information (demographics, drugs dispensed and procedures) and all inpatient information (expensive drugs dispensed, procedures performed during hospital stays and diagnoses).<sup>26</sup> Studies based on this database have produced meaningful results in recent years.<sup>27–30</sup>

We adapted an algorithm previously used<sup>30,31</sup> to identify pregnancies ending between 1 January 2010 and 31 December 2019 among women aged 15–49 years in the SNDS. The pregnancy end date was the date of delivery, or, when missing, the date of admission for pregnancy completion. The date of conception was calculated using gestational age at the end of pregnancy, or, when missing, the date of the last menstrual period entered by the physician at the end of pregnancy.<sup>32</sup>

### 2.2 | Study population

All pregnancies whose duration was >88 days (12 weeks + 4 days of amenorrhoea) and that ended between January 2010 and December 2019 were included. Because most first trimester spontaneous abortions are not identifiable in the French national health data system, we excluded pregnancies lasting <88 days in the main analysis, as done in previous studies.<sup>8</sup> In case of multiple pregnancies during the same calendar year, the first pregnancy was considered. Pregnancy outcomes were livebirth, stillbirth (defined by the delivery of a dead foetus after 22 weeks of amenorrhoea), spontaneous abortion (defined by delivery of a foetus with gestational age <22 weeks of

amenorrhoea) and medical termination of pregnancy (termination of pregnancy for maternal health or foetal disease).

## 2.3 | AI agents

We considered the following pharmacological classes of AI agents according to the Anatomical Therapeutic Chemical classification<sup>33</sup>: systemic antibacterials, systemic antivirals and influenza vaccine, systemic and intravaginal antifungal agents and antiparasitic agents. Subgroups of each category are detailed in Table S1.

Potentially harmful AI agents were identified using the classification systems of the ADEC and the FASS. We considered as potentially harmful those AI agents with either a FASS D classification or an ADEC D or X classification as previously described.<sup>34</sup> For example, doxycycline is classified as potentially harmful in both systems (D; Tables S2, S3).

For each pregnancy, up to 7 trimesters were studied: 2 trimesters before the beginning of pregnancy (T-2: day -182 to day -92; T-1: day -91 to day -1), each trimester of pregnancy (T1: day 0 i.e., date of conception to day 90; T2: day 91 to day 181; T3: day 182 to delivery -1) and 2 trimesters after the end of pregnancy (T+1: delivery to delivery + 91; T+2: delivery + 92 to delivery + 182). The pregnancy trimesters (T1 to T3) were defined as the whole pregnancy period. We considered exposure during a trimester of pregnancy when this drug was dispensed at least once during this trimester. We assumed that medications were used the trimesters they were dispensed.

## 2.4 | Statistical analysis

The unit of analysis was a pregnancy. For each AI agent of interest, the prevalence rate, estimated as the number of pregnancies with exposure to the AI agent per 100 pregnancies, was computed over the whole period of the pregnancy (from T1 to T3) and separately across each trimester before, during and after pregnancy. To estimate the trends in prevalence rates from 2010 to 2019, Joinpoint regression models were applied using the Joinpoint Regression Program, version 4.7.0.0 (Statistical Research and Applications Branch, National Cancer Institute, Bethesda, MD, USA). We used the average annual percentage change (AAPC), a summary measure of the trend over a fixed time interval. The AAPC is computed as follows: changes in trends over time are estimated using Joinpoint regression approach in which data are divided into subsets, where each subset has its own linear trends. The AAPC over any pre-fixed time interval is then calculated using the weighted average of the slope coefficient of the underlying joinpoint regression model and then transforming the weighted average to an annual percent change. AAPC is a valid measure even if the joinpoint model reveals changes in trends over the years. The 95% confidence interval (CI) of the AAPC was also calculated in the regression model, as well as the corresponding *P*-value. The prevalence of an AI agent was considered showing an upward trend if the estimated AAPC was positive and the corresponding

*P*-value was <.05. In contrast, this prevalence was considered showing a statistically significant downward trend if the estimated AAPC was negative and the corresponding *P*-value was <.05. We performed a sensitivity analysis excluding pregnancies of <259 days (39 weeks of amenorrhoea) to account for potential differences in length of the second and/or third trimester in case of preterm birth.

## 2.5 | Ethics

The French public institution which conducted this study has permanent access to the SNDS database in application of the provisions of Articles R. 1461-12 et seq. of the French Public Health Code and the French data protection authority decision CNIL-2016-316. No informed consent was therefore required. This research did not receive any funding.

## 3 | RESULTS

Of a total of 9 905 501 pregnancies ending between 2010 and 2019 in France, the 7 571 035 pregnancies of at least 88 days duration and not voluntarily terminated were included (Figure S1). Among these 7 571 035 pregnancies, 7 432 532 (98.17%) resulted in livebirths, 38 619 (0.51%) in stillbirths, 35 930 (0.47%) in spontaneous abortions and 63 954 (0.84%) in medical termination of pregnancy. The annual number of pregnancies included decreased from 797 971 in 2010 to 697 767 in 2019.

### 3.1 | Use of systemic antibacterial agents

Over the 2010-2019 period, 3 027 031 (40.0%) pregnant women received at least 1 systemic antibacterial. Amoxicillin was by far the most commonly prescribed antibacterial (24.0% of all pregnancies). From 2010 to 2019, the overall prevalence of systemic antibacterial use (per 100 deliveries) decreased from 41.5 to 36.1% (AAPC = -1.7%, [95%CI, -2.5 to -1.0%]; Table 1). This decrease concerned penicillins, cephalosporins, quinolones, macrolides, aminoglycosides, tetracyclins and nitrofurantoin and not Fosfomycin, exposure of which increased, particularly after 2015 (AAPC = 10.7%, [95%CI, 6.9 to 14.6%]; Figure 1).

Antibacterial agent use varied during the course of pregnancy. Exposure to antibacterials was less frequent during pregnancy (particularly during the third trimester) than during the prepregnancy period (T-2 and T-1) with however some particularities according to classes considered (Figure 2): exposure to penicillin (mainly amoxicillin) increased during the first 2 trimesters of pregnancy (11.4% in T1 and 13.0% in T2) and the immediate postpartum trimester (12.8% in T+1) as compared to the prepregnancy period (9.7% for T-2 and T-1). Exposure to nitrofurantoin and fosfomycin (the latter for the year 2019) increased during the first two trimesters of pregnancy as compared to pre- and postpregnancy periods (Figure 2 and Figure S2).

**TABLE 1** Prevalence of anti-infective agents use during pregnancy by calendar year and average annual percent change (AAPC), France, 2010–2019

	2010		2011		2012		2013		2014		2015		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
<b>Systemic antibacterials</b>	331 327	(41.5)	335 489	(42.4)	328 809	(41.7)	322 647	(41.5)	311 321	(40.0)	307 107	(40.5)	
Penicillins	231 547	(29.0)	237 968	(30.1)	232 554	(29.5)	233 294	(30.0)	218 472	(28.1)	213 735	(28.2)	
Cephalosporins	59 600	(7.5)	62 064	(7.8)	65 053	(8.2)	57 383	(7.4)	66 968	(8.6)	69 549	(9.2)	
Quinolones	8739	(1.1)	8720	(1.1)	8498	(1.1)	9045	(1.2)	8507	(1.1)	7576	(1.0)	
Macrolides	71 295	(8.9)	69 827	(8.8)	65 814	(8.3)	61 137	(7.9)	54 934	(7.1)	53 708	(7.1)	
Aminosides	916	(0.1)	682	(0.1)	590	(0.1)	548	(0.1)	345	(0.0)	418	(0.1)	
Tetracyclines	3502	(0.4)	3462	(0.4)	3542	(0.4)	3394	(0.4)	3480	(0.4)	3197	(0.4)	
Fosfomycin	31 151	(3.9)	30 226	(3.8)	30 172	(3.8)	29 839	(3.8)	30 196	(3.9)	29 423	(3.9)	
Nitrofurantoin	16 155	(20.2)	16 635	(21.0)	14 132	(17.9)	14 802	(19.0)	13 398	(17.2)	13 919	(18.3)	
<b>Antiviral agents</b>													
Anti HSV agents	9188	(1.2)	9494	(1.2)	9988	(1.3)	10 314	(1.3)	10 799	(1.4)	11 428	(1.5)	
HIV-ART agents	1425	(0.2)	1445	(0.2)	1488	(0.2)	1479	(0.2)	1461	(0.2)	1532	(0.2)	
Anti influenza agents	18 688	(2.3)	4089	(0.5)	1381	(0.2)	2587	(0.3)	1148	(0.1)	3057	(0.4)	
Influenza vaccine	1902	(0.2)	2520	(0.3)	2760	(0.3)	4665	(0.6)	6969	(0.9)	8837	(1.2)	
<b>Antifungal agents</b>													
Intravaginal antifungals	228 424	(28.6)	229 308	(29.0)	228 147	(28.9)	234 458	(30.1)	233 820	(30.1)	224 929	(29.6)	
Systemic antifungals	4014	(0.5)	4551	(0.6)	4813	(0.6)	4879	(0.6)	5229	(0.7)	5851	(0.8)	
<b>Anti-parasitic agents</b>													
Pyrimethamine + Sulfadiazine	205	(0.0)	125	(0.0)	148	(0.0)	140	(0.0)	136	(0.0)	169	(0.0)	
Spiramycin	25 269	(3.2)	23 761	(3.0)	20 839	(2.6)	18 583	(2.4)	15 346	(2.0)	14 098	(1.9)	
<sup>a</sup> Average annual percentage change.													
<b>TABLE 1 (Continued)</b>													
	2016		2017		2018		2019		AAPC <sup>a</sup>		95% CI		P-value
	N = 742 187		N = 723 976		N = 713 420		N = 697 767						
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
<b>Systemic antibacterials</b>	296 190	(39.9)	275 767	(38.1)	266 231	(37.3)	252 143	(36.1)	-1.7	-2.5	-1.0	<.001	
Penicillins	208 065	(28.0)	193 272	(26.7)	186 008	(26.1)	174 315	(25.0)	-1.8	-2.5	-1.1	<.001	
Cephalosporins	60 291	(8.1)	44 843	(6.2)	37 832	(5.3)	32 298	(4.6)	-5.2	-8	-2.3	.001	
Quinolones	7101	(1.0)	6362	(0.9)	5586	(0.8)	4905	(0.7)	-4.6	-6	-3.1	<.001	
Macrolides	49 638	(6.7)	43 649	(6.0)	41 237	(5.8)	37 914	(5.4)	-5.6	-6.2	-5.0	<.001	
Aminosides	383	(0.1)	311	(0.0)	162	(0.0)	68	(0.0)	-22.4	-30.2	-13.6	<.001	

TABLE 1 (Continued)

	2016		2017		2018		2019		AAPC <sup>a</sup>	95% CI	P-value
	n	(%)	n	(%)	n	(%)	n	(%)			
	N = 742 187		N = 723 976		N = 713 420		N = 697 767				
Tetracyclines	2954	(0.4)	2727	(0.4)	2603	(0.4)	2418	(0.3)	-2.6	-3.2	<.001
Fosfomycin	36 476	(4.9)	50 793	(7.0)	57 309	(8.0)	59 875	(8.6)	10.7	6.9	<.001
Nitrofurantoin	12 688	(17.1)	8245	(11.4)	6692	(9.4)	5670	(8.1)	-10.5	-13.1	<.001
<b>Antiviral agents</b>											
Anti HSV agents	11 643	(1.6)	11 889	(1.6)	11 763	(1.6)	11 809	(1.7)	4.4	3.7	<.001
HIV-ART agents	1463	(0.2)	1510	(0.2)	1395	(0.2)	1393	(0.2)	1.3	0.6	.003
Anti influenza agents	3151	(0.4)	3735	(0.5)	4747	(0.7)	6038	(0.9)	25.4	6.2	.017
Influenza vaccine	11 178	(1.5)	17 147	(2.4)	30 027	(4.2)	58 847	(8.4)	49.7	39.3	<.001
<b>Antifungal agents</b>											
Intravaginal antifungals	215 009	(29.0)	203 007	(28.0)	194 784	(27.3)	182 630	(26.2)	-0.8	-1.3	.001
Systemic antifungals	7176	(1.0)	7798	(1.1)	9110	(1.3)	9012	(1.3)	11.8	9.8	<.001
<b>Anti-parasitic agents</b>											
Pyrimethamine + Sulfadiazine	139	(0.0)	110	(0.0)	123	(0.0)	109	(0.0)	-2.7	-6.3	.133
Spiramycin	12 362	(1.7)	10 199	(1.4)	8665	(1.2)	7521	(1.1)	-11.6	-12.4	<.001

<sup>a</sup> Average annual percentage change.

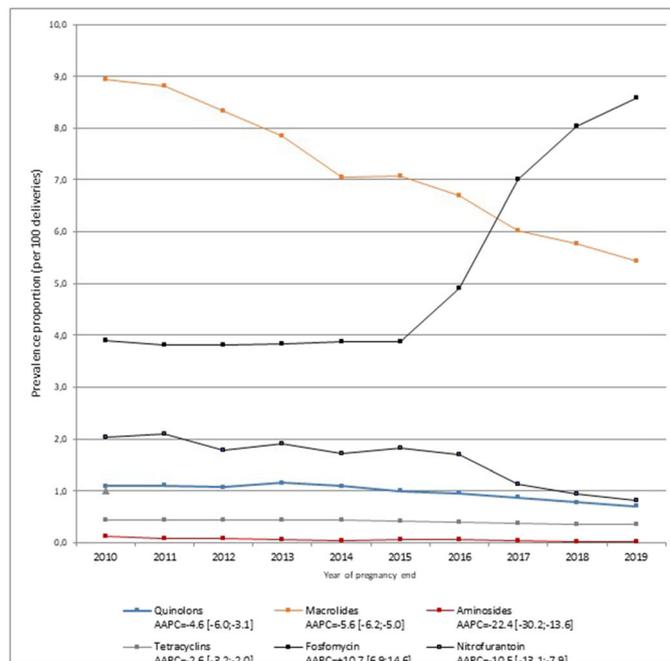
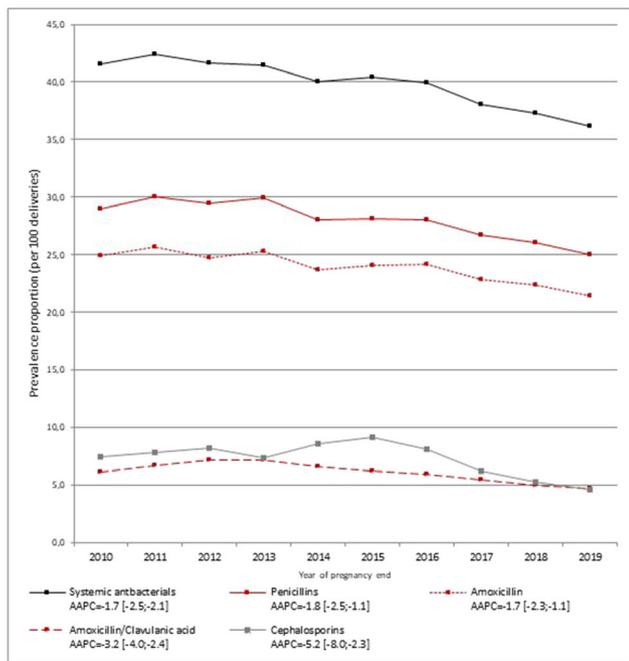


FIGURE 1 Prevalence of systemic antibacterials use during pregnancy by calendar year, France, 2010–2019

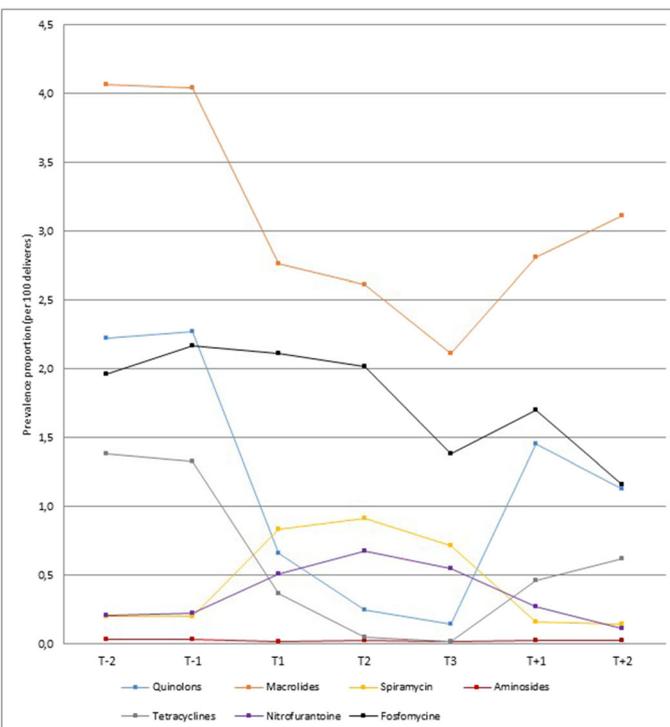
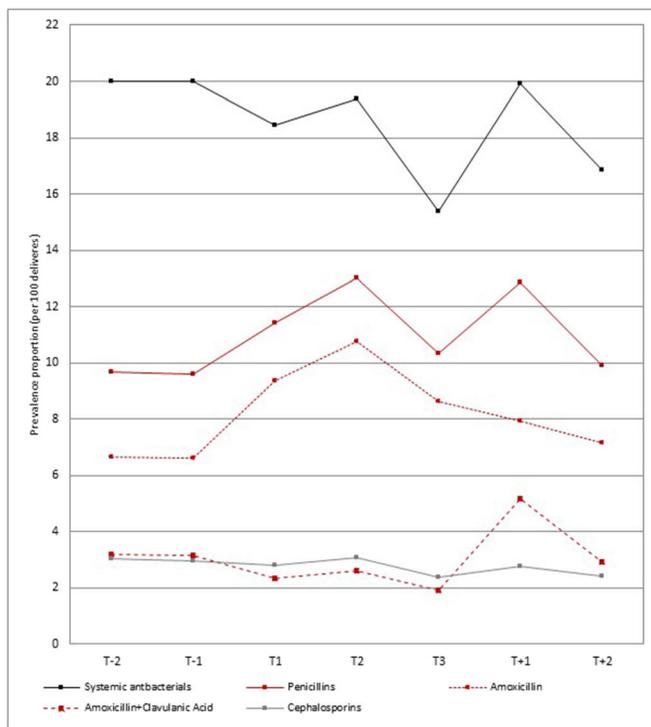


FIGURE 2 Prevalence of systemic antibacterials use per trimester of pregnancy, France, 2010–2019

### 3.2 | Use of antiviral agents

Antiviral agent' use increased during the 10 years' study period for anti-herpes simplex virus (HSV) agents (AAPC = 4.4%, [95%CI, 3.7 to 5.2%]), for influenza agents (AAPC = 25.4%, [95%CI, 6.2 to 48.1%])

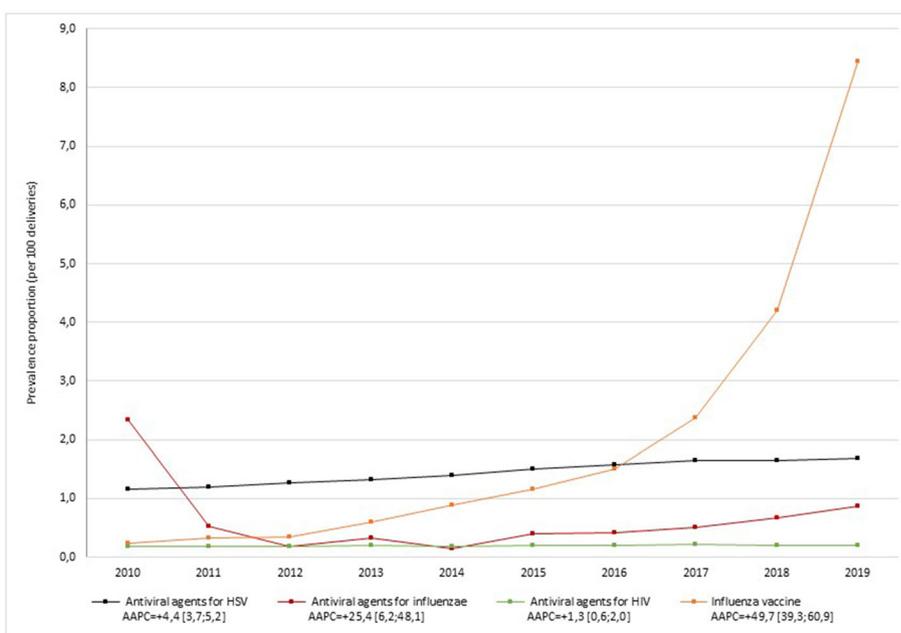
and for HIV-antiretroviral treatments (HIV-ART; AAPC = 1.3%, [95% CI, 0.6 to 2.0%]; Table 1 and Figure 3). Among HIV-ART agents, exposure to both nucleoside reverse transcriptase inhibitors (NRTIs) and non-NRTIs, when not dispensed in single-tablet combination, decreased (AAPC = -7.0%, [95%CI, -11.5 to -2.3%]) for non-NRTIs;

AAPC = -1.7%, [95%CI, -2.7 to -0.8%]) for NRTIs whereas exposure to HIV-ART as single-tablet combination sharply increased AAPC = 30.8%, [95%CI, 27.5 to 34.3%]; Figure S4). Use of influenza vaccine during pregnancy increased from 0.2% in 2010 to 4.2% in 2019 (AAPC = 49.7%, [95%CI, 39.3 to 60.9%]).

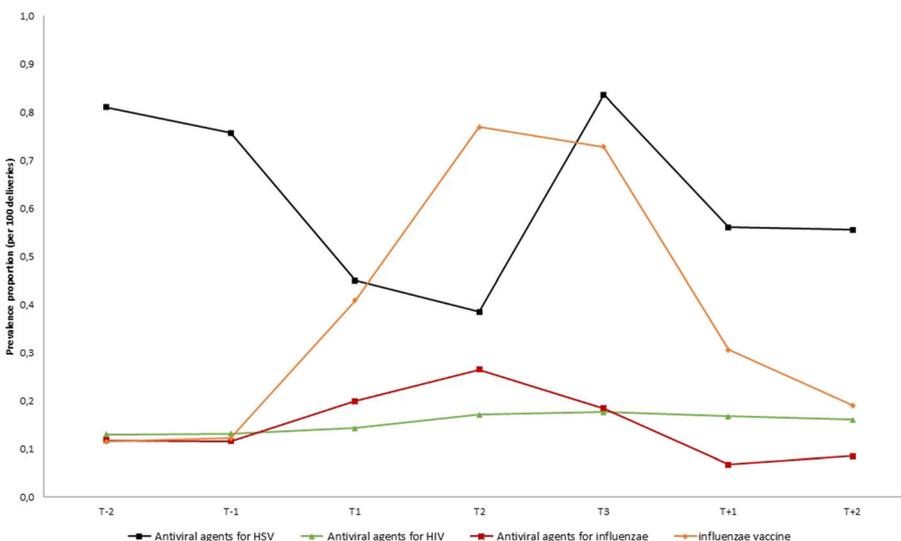
Exposure to both influenza agents and vaccine increased during pregnancy as compared to pre- and postpregnancy periods (Figure 4). Exposure to anti-HSV agents decreased during the first 2 trimesters (T1 and T2) as compared to the pre- and postpregnancy periods. Among HIV-ART, use of both NRTI and protease inhibitors increased during the course of pregnancy as compared to the pre- and postpregnancy periods (Figures S5-S6).

### 3.3 | Use of antifungal and antiparasitic agents

Over the 2010–2019 period, 2 174 516 (28.7%) and 62 433 (0.8%) pregnant women received at least 1 intravaginal and 1 systemic antifungal agent, respectively. Use of intravaginal antifungal slightly decreased during the 10 years' study period (AAPC = -0.8%, [95%CI, -1.3 to -0.3%]), whereas use of systemic antifungal markedly increased (AAPC = 11.8%, [95%CI, 9.8 to 13.8%]; Table 1). During pregnancy, use of intravaginal agents continuously increased from 8.6% in the first trimester to 16.0% in the third trimester and was higher than during the pre- and postpregnancy periods (4.6% in T-1 and 4.9% in T+1). Exposure to systemic antifungal agents slightly



**FIGURE 3** Prevalence of antiviral agents use during pregnancy by calendar year, France, 2010–2019



**FIGURE 4** Prevalence of antiviral agents use per trimester of pregnancy, France, 2010–2019

decreased from 0.33% in the first trimester to 0.29% in the third trimester and was lower than during the pre- and postpregnancy periods (0.71% in T-1 and 1.07% in T+1).

Over the 2010–2019 period, exposure to combination of pyrimethamine and sulfadiazine, generally used as foetal therapy in case of congenital toxoplasmosis remained stable (0.02%) while exposure to spiramycin, mainly indicated to prevent maternal–foetal toxoplasmosis transmission decreased from 3.2% in 2010 to 1.1% in 2019 (AAPC =  $-11.6\%$ , [95%CI,  $-12.4$  to  $-10.8\%$ ]; Table 1). Combination of pyrimethamine and sulfadiazine was only used in the third trimester of pregnancy (0.02%) whereas exposure to spiramycin increased during the first 2 trimesters (0.8% in T1, 0.9% in T2) as compared to pre- and postpregnancies periods (0.2% in T-2 and T-1, 0.2% in T+1, 0.1% in T+2). Combination of pyrimethamine and sulfadiazine was not used during the pre- and postpregnancy periods.

### 3.4 | Use of potentially harmful AI agents

Among all pregnancies, 0.9% had been exposed to a potentially harmful AI agent increasing from 0.7% ( $n = 5865$ ) in 2010 to 1.2% ( $n = 8351$ ) in 2019 (AAPC =  $6.4\%$ , [95%CI,  $4.4$  to  $8.5\%$ ]). In more detail, the most frequently used potentially harmful AI agents during the 2010–2019 period were doxycycline ( $n = 25\,130$ ; 0.3%) with a decreasing trend (AAPC =  $-1.8\%$ , [95%CI,  $-2.5$  to  $-1.1$ ]) and fluconazole ( $n = 24\,752$ ; 0.3%) with an increasing trend (AAPC =  $24.4\%$ , [95%CI,  $3.7$  to  $49.3\%$ ]; Table S4). Exposure to potentially harmful AI agents was highest during the pre- and postpregnancy periods (1.9% in T-2 and T-1 and 0.9% in T+1 and 1.0% in T+2) and decreased during pregnancy from 0.6% in the first trimester to 0.2% in the third trimester.

Results of the sensitivity analysis after exclusion of pregnancies lasting <259 days were similar (data not shown).

## 4 | DISCUSSION

### 4.1 | Principal findings

In this nationwide population-based study of more than 7 million pregnancies over a 10-year period, we found: (i) a high prevalence of systemic antibacterials use during pregnancy, but a significant decrease over time; (ii) conversely, use of anti-HSV agents, influenza antiviral agents and vaccine, HIV-ART agents, and systemic antifungals increased over time; and (iii) although use of potentially harmful AI agents decreased during the course of pregnancy, their use during pregnancy increased significantly over the 2010–2019 period.

### 4.2 | Results in the context of what is known

The prevalence rate of 40% for systemic antibacterials during pregnancy (T1–T3) was in the upper range of that described in other

countries, where rates varied between 20.8% in the Netherlands<sup>3</sup> and 49.7% in the USA.<sup>8</sup> However, we observed a significant decrease over the last decade with an average annual percent change of  $-1.7\%$ , [95%CI,  $-2.5$  to  $-1.0\%$ ]. This trend was observed for most categories of antibacterials with the exception of Fosfomycin, whose exposure has markedly increased. In France, fosfomycin became the first-line recommended treatment<sup>35</sup> in cystitis during pregnancy in 2015. The downward trend for systemic antibacterials was also observed during pre- and postpregnancy periods (data not shown), as recently described in France outside pregnancy.<sup>36</sup> To our knowledge, our study is the first to show such a downward trend. Other studies<sup>3,9,16</sup> have mostly reported an increasing trend but comparisons are difficult because these studies concerned an earlier period prior to 2010.

Another notable finding was the higher exposure to penicillins (mainly driven by amoxicillin) throughout pregnancy as compared to exposure during pre- and postpregnancy periods. Other classes of antibacterial such as quinolones, macrolides and tetracyclines showed on the contrary a trend toward a decrease during the pregnancy period. Similar results were observed in other studies.<sup>3,11</sup>

Concerning antiviral agents and specifically influenza agents, as pregnancy is a risk factor for severe outcomes,<sup>37</sup> several public policies recommend influenza vaccine during pregnancy and treating pregnant women with influenza agents (i.e., neuraminidase inhibitors).<sup>38,39</sup> In accordance with these national recommendations, both influenza vaccine and neuraminidase inhibitors showed a higher frequency of use during pregnancy as compared to pre- and postpregnancy periods. In addition, we found marked increases in the use of both influenza vaccine (average annual increase of 50%) and neuraminidase inhibitors exposure (average annual increase of 25%) over the last decade. The latter started in 2012, after a very high prevalence rate in 2010 following the 2009 pandemic of H1N1 influenza. Despite these increases, influenza vaccination rate remained low (8.4% in 2019). This is in line with results from a cross-sectional study conducted in France in 2016 in which vaccine coverage among pregnant women was estimated around 7%,<sup>40</sup> that is, a lower rate than those reported in other high-income countries, reaching 18–30% in the USA<sup>41</sup> and around 40% in the UK.<sup>42</sup>

HIV antiretroviral agents have increased moderately during the last decade. This trend is difficult to link with the evolution of the epidemiology of HIV because it is not possible to distinguish treatments of women previously diagnosed and treated and those of newly diagnosed women with initiation of treatment during pregnancy. The increase between the trimester before pregnancy and the first 2 trimesters of pregnancy might be explained by the French recommendation to screen all pregnant women during the first trimester of pregnancy.<sup>43</sup> Antiviral agents for HSV also increased over the past 10 years with highest frequency of use in the third trimester of pregnancy, that may reflect the antiviral prophylaxis' guidelines to treat women in case of first or recurrent episode of genital herpes during pregnancy from 36 weeks of gestation until delivery.<sup>44</sup>

In addition, antifungal agents were commonly used during pregnancy with an upward trend for systemic antifungals over the last

10 years. Although intravaginal formulations of topical azoles are first-line treatment during pregnancy, oral fluconazole is used in cases of recurrence, severe symptoms, or when topical treatment has failed; they may also be used as the first treatment by personal preference.<sup>45</sup> However, data regarding safety use of fluconazole during pregnancy have been controversial because of the conflicting reports of teratogenicity and risk of spontaneous abortion and stillbirth.<sup>19</sup> The observed increasing trend of potentially harmful agents during the last decade is mainly driven by the use of systemic antifungals (fluconazole) during pregnancy.

### 4.3 | Clinical implications

The downward trend in systemic antibacterials that we are the first to observe might be explained by progressive efforts to combat emergence of antimicrobial resistances,<sup>46</sup> which should be encouraged in all countries.

The decreased use of many antibacterial agents during pregnancy can probably be explained by several factors: the potential harmful risk of tetracyclines; the conflicting results on macrolide–quinolone association; risk of miscarriage or birth defects.<sup>12–15,17,18,47,48</sup> Prescribers would probably prefer using safer alternatives once pregnancy is identified such as penicillins. On the contrary, we identified antibacterials more often used during pregnancy than outside of pregnancy, which could be related to indications more frequent during pregnancy such as urinary tract infections (nitrofurantoin and fosfomycin), or prevention of foetal disease such as congenital toxoplasmosis in case of maternal seroconversion (spiramycin).

Several prescription patterns reported in our study probably reflect the adherence of physicians to recommendations of use for pregnancy: fosfomycin as cited above, antiretroviral agents for HIV and antiviral agents for HSV. The same is true for influenza agents (neuraminidase inhibitors and vaccine) but with a long delay in implementation when compared to other European countries. This delay may be explained by poor vaccine acceptance in the French population.<sup>49</sup>

### 4.4 | Strengths and limitations

The present study has a number of major strengths. First, it is based on a large and unselected cohort of pregnant women during recent years. Second, the French national health data system is a comprehensive database for drug dispensing, covering more than 99% of the French population (around 66 000 000 people). Third, we used definitions for AI agents based on third level of Anatomical Therapeutic Chemical classification allowed us to study subgroups and AI agents in detail.

This study also has certain limitations. First, like previously published studies based on the SNDS databases, algorithms rather than clinical data were used to identify pregnancies. Nevertheless, the

validity of algorithms has previously been demonstrated.<sup>30–32</sup> Second, a dispensed drug does not mean that it has been used. However, studying dispensed drugs and not prescriptions avoids primary non-compliance, that is, the patient does not redeem the prescription. Third, there was no information available on drug indication, which did not make possible the evaluation of adherence to the recommendations for systemic antibacterials. Nevertheless, we used information on the safety categories according to the Swedish or Australian systems to evaluate the propensity of physicians to generally avoid prescription of potentially harmful drugs, whatever the indication. Finally, prevalence rates may have been underestimated in the first trimester because of exclusion of pregnancies with duration <88 days; this could also be the case during the third trimester, which could be shorter in case of preterm birth. However, the sensitivity analysis restricting to pregnancies of 259 days (39 weeks of amenorrhoea) or more showed similar results for all AI-agents, which confirmed that this limitation has little impact on our results.

### 4.5 | Conclusion

Our study shows a high prevalence of systemic antibacterials use during pregnancy in France during the 2010–2019 period, but also a decrease that had never been shown before. This decrease may be related to recommendations promoting a reduction in antibiotic use, as observed in France in the general population. Our results also suggest a potential for improvement in influenza vaccination. Such studies are thus important to show the impact of recommendations and target future public policies in order to optimize safe and efficient treatments for pregnant women.

#### COMPETING INTERESTS

The authors declare no conflicts of interest.

#### CONTRIBUTORS

S.T. made a substantial contribution to conception and design, data analysis and interpretation, drafting of the article and approved the manuscript before submission. J.S. made a substantial contribution to conception and design, data interpretation, drafting of the article and approved the manuscript before submission. P.H. made a substantial contribution to the data acquisition and analysis, and approved the manuscript before submission. J.D. made a substantial contribution to the data acquisition and analysis, and approved the manuscript before submission. O.P. made a substantial contribution to interpretation of the data and approved the manuscript before submission. X.D. made a substantial contribution to interpretation of the data, drafting of the article and approved the manuscript before submission. A.W. made a substantial contribution to conception and design and approved the manuscript before submission. M.Z. made a substantial contribution to conception and design and approved the manuscript before submission. R.D.S. made a substantial contribution to conception and design, data interpretation, drafting of the article and approved the manuscript before submission.

## DATA AVAILABILITY STATEMENT

The procedures carried out with the French data privacy authority (CNIL, Commission nationale de l'informatique et des libertés) do not provide for the transmission of the database. Consultation by the editorial board or interested researchers may nevertheless be considered, subject to prior determination of the terms and conditions of such consultation and in respect for compliance with the applicable regulations. All requests for access must be submitted to the Health data hub. Further information to do this request is available on these websites:

- <https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees>
- <https://documentation-snds.health-data-hub.fr/introduction/03-acces-snds.html#les-acces-sur-projet>

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## SUPPORTING INFORMATION

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