An efficient cephalosporin stewardship programme in French swine production

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Abstract

By 2010, systems set up to monitor the antimicrobial resistance of pathogenic bacteria and antimicrobial usage identified a sustained increase regarding third- and fourth-generation cephalosporin resistance in French pig production. This sector mobilised and collectively committed to responsible action in the following months. This led to a multi-professional voluntary stewardship programme that was started in 2011. A consensus of veterinary opinion led to the definition of restrictive rules on the prescription of the third- and fourth-generation cephalosporins targeted by the antimicrobial stewardship programme (ASP). All pig sector professionals, including farmers, were informed. Existing monitoring systems for usage and resistance were supplemented by data from the records of veterinarians' cephalosporin deliveries and from individual pig farm surveys investigating antimicrobial usage. The second step, from 2014, entailed regulatory measures that consolidated the programme by setting quantitative reduction objectives and specifying the terms and conditions for prescribing and dispensing a list of critical antimicrobial molecules including cephalosporins. All the data sources confirmed a significant fall of more than 90% in cephalosporin usage in the French pig production sector between 2010 and 2016. Monitoring systems recorded that the resistance of commensal and pathogenic *Escherichia coli* isolates also tended to decrease over the same period. The stewardship programme proved highly effective in reducing usage and containing resistance, illustrating the efficiency of a well-defined multi-professional strategy.

KEYWORDS

antimicrobial stewardship, cephalosporin resistance, *Escherichia coli*, One Health

1 | INTRODUCTION

In a 'One Health' perspective, it has been widely advised to reduce the usage of antimicrobials, especially those considered as critically important for human health. Antimicrobial stewardship programmes (ASPs) are, therefore, encouraged in a variety of environments, including hospital, community and agricultural settings (McEwen & Collignon, 2018). Although the contents of such programmes in

hospitals have been frequently reviewed (e.g. Davey et al., 2017), the setting up of ASPs can also be envisioned in a broader perspective (Dyar et al., 2017), including veterinary medicine. A practical example of an ASP targeting cephalosporins in veterinary medicine is reported hereafter, from its genesis, definition, implementation and follow-up to an impact assessment in order to highlight its critical points (Turnidge, 2015) and animal agriculture possible contribution to a One Health approach of antimicrobial resistance (Gray & Mazet, 2020).

Impacts

- This study details conditions for success of an antimicrobial stewardship programme in animal agriculture
- Based on data provided by complementary and independent monitoring tools, success could be assessed in terms of both antimicrobial usage and resistance
- Results highlight the strong relationship between cephalosporin usage and resistance in pig production, supporting a containment perspective through usage restriction.

1.1 | Genesis

In 2008, the national surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin, RESAPATH alerted pig production stakeholders of a sudden increase in the number of pathogenic *Escherichia coli* isolates non-susceptible to ceftiofur, a third-generation cephalosporin (RESAPATH, 2011). The data collected revealed that these non-susceptible bacteria were mainly isolated from piglets suffering from digestive disorders and rarely from sows. This observation was first addressed within the RESAPATH network before related information was subsequently circulated and shared with the pig industry through various meetings.

The data on sales of veterinary medicinal products containing antimicrobials showed that cephalosporins represented a small proportion of antimicrobial usage in swine production (Chevance & Moulin, 2014). After an abrupt increase in 2006, the two compounds authorised for swine – ceftiofur and cefquinome – never accounted for more than 0.3% and 1.3% of the estimated amount of ADDkg and ACDkg (Animal Daily Dose and Animal Course Dose measuring, respectively, the live weight exposed and treated [Meheust et al., 2017]) sold in 2010. However, an on-farm usage survey revealed that suckling piglets were the main category of animals treated with these compounds in 2008 (Chauvin, 2010), some of the corresponding treatments being preventive and typically repeated on successive batches to limit arthritis. Although the corresponding live weight treated was limited, many animals were actually concerned.

Interestingly, consistent observations were reported elsewhere during the same time span. A marked increase in the use of cephalosporins was observed mainly in sows and piglets in Denmark during the 2000s, suggesting a shift away from occasional to systematic use (DANMAP, 2007). The prophylactic use of cephalosporins in piglets was found to be statistically significantly associated with the occurrence of reduced susceptibility in *E. coli* (Jørgensen et al., 2007). The selection of resistant strains following treatment (Cavaco et al., 2008) and possible transmission to humans was also documented (Moodley & Guardabassi, 2009).

Considering (a) the national and bibliographical data underpinning an increase in bacterial resistance in relation with usage, and (b) the critical importance of cephalosporins in human medicine (Collignon et al., 2009; Scientific Advisory Group on Antimicrobials of the Committee for Medicinal Products for Veterinary Use, 2009), the French pig production sector's reaction was to commit to responsible action. A specific meeting was organised in 2010 to address the issue. Participants included representatives of swine production veterinary practitioners (AFMVP: French Association of Swine Veterinarians; AVPO: Association of Veterinarians practising in animal production; SNGTV: French National Society of Veterinary Technical Groups), and swine producers and production organisations (INAPORC, the French Interprofessional Pork Organisation that brings together the professional federations representing animal manufacturers, pork producers, slaughterers, processors and delicatessen dealers; COOP DE FRANCE: a cooperative association representing the interests of agricultural cooperatives and FNP: the French pig producers' federation). Agreement was reached on implementing a voluntary stewardship programme designed to restrict the use of third- and fourth-generation cephalosporins in French pig production.

2 | MATERIALS AND METHODS

2.1 | Professional voluntary stewardship programme

The programme was officially announced at the French event organised on antibiotic awareness day, 18 November 2011 (Figure 1), but implementation had already begun during the first semester of 2011. Its components (Figure 2, Table 1) included:

1. The rules regarding cephalosporin prescription and usage were clearly defined through a veterinarian consensus-building process (Chouet et al., 2012). An ad hoc working group of veterinary practitioners agreed that cephalosporins should never be used as first-line antibiotics or for systematic usage. An antimicrobial susceptibility testing result showing that no other compound was effective should precede and justify any prescription. The one exception to this rule is an emergency curative intervention for acute respiratory disorders due to *Actinobacillus pleuropneumoniae* occurring during the last fattening phase. All swine practitioners received these rules (see point 3 below), which were also promoted during professional meetings. Additionally, an article detailing both the rationale and alternatives to past

indications for cephalosporins was published to provide guidance to veterinary practitioners (Le Coz et al., 2012).

2. A letter was sent to all French pig producers by the Interprofessional organisation in May 2011 explaining the stewardship programme's aim (i.e. to protect the efficacy of a critically important antibiotic for human medicine) and application. It highlighted the strong support received for the measures from both the producers' organisations and the veterinarians. This information reinforced oral and written explanations given on every production site through veterinary visits and the newsletters of pig production organisations.
3. Representatives of veterinary practitioners voluntarily decided to allow their compliance with the rules to be monitored (Chouet et al., 2012). The veterinarian associations appointed for this purpose, the CTPA (*Centre Technique des Productions Animales*), an independent body, which (a) contacted all swine practitioners to collect their formal commitment to abide by the consensus, and (b) analysed the annual statistics on cephalosporin deliveries provided by veterinarians for 2010, 2011 and 2012 in order to check the compliance with cephalosporin usage restrictions.
4. A survey to monitor antimicrobial use was also set up on a representative sample of French pig farms. The survey, funded by INAPORC and carried out by the French Pork and Pig Institute (IFIP), was first done in 2011, then repeated in 2014 and 2017. It retrospectively covered 2010 (and 2013 and 2016 respectively), providing information on the antimicrobial usage of about 150 randomly selected farms through both sales and delivery data and farmer interviews (Hemonic et al., 2018).

2.2 | National legislative and administrative measures

A 5-year national plan to reduce antimicrobial usage was launched by the French Ministry of Agriculture, Agro-Food and Forestry on 18 November 2011 for the 2012–2016 period (Ministry of Agriculture, Agro-Food, & Forestry, 2016). This public policy aimed to both reduce the exposure of animals to antibiotics by 25% within a 5-year period and to durably preserve the therapeutic arsenal of antibiotics. The plan comprised 40 detailed measures to promote good practices, raise the awareness of stakeholders, develop alternatives, reinforce regulations and improve monitoring systems on antimicrobial resistance and use.

To strengthen the relevant legislation, in October 2014 the Law on the future of agriculture, food and forestry was adopted. The target of Article 49 was a 25% reduction in the use of critical antibiotics (i.e. fluoroquinolones and third- and fourth-generation cephalosporins) in veterinary medicine by 2016 (3 years). Decree no. 2016-317 and the Order of 18 March 2016 then specified the terms and conditions for prescribing and dispensing a list of specific molecules. Critical antibiotics were banned for preventive purposes and

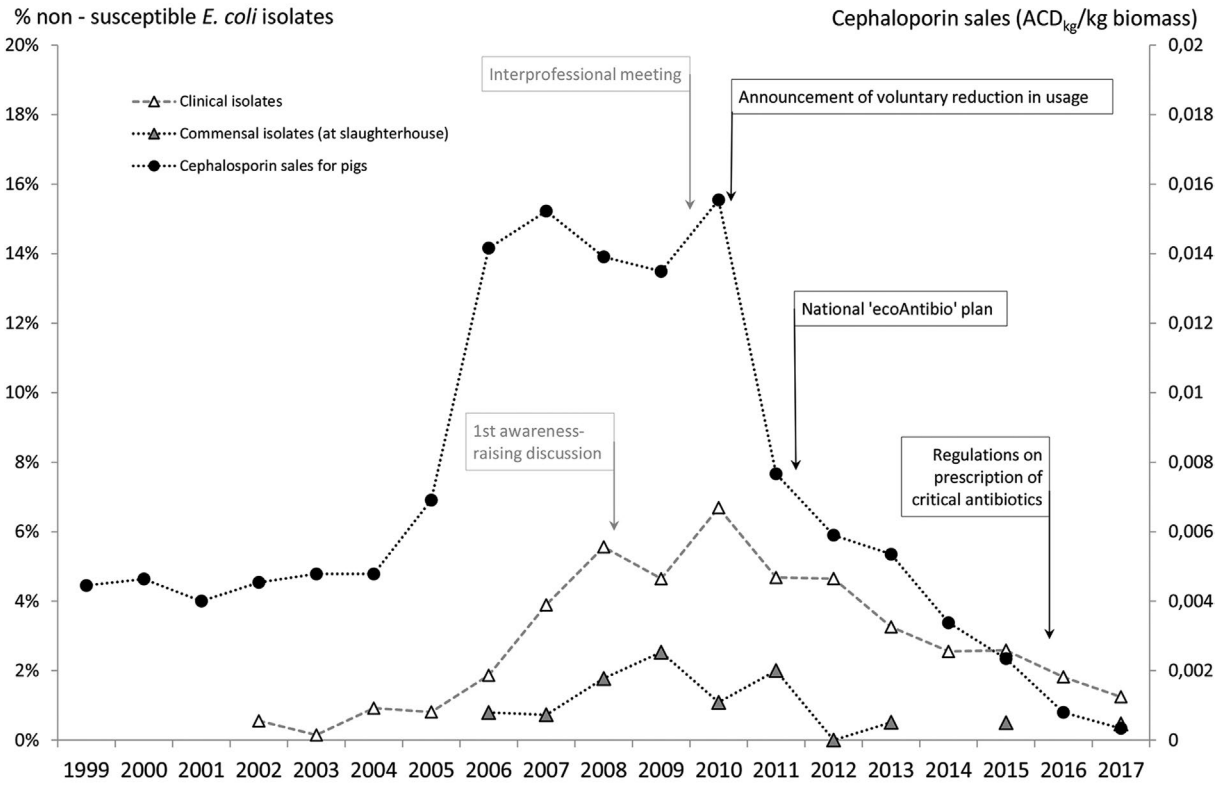

FIGURE 1 Evolution of national sales of cephalosporin for pigs (expressed as the amount of live weight treated (in animal course dose or ACDkg) related to the biomass produced and present, in kg) and percentages of non-susceptible clinical and commensal pig *Escherichia coli* isolates in France from 1999 to 2017, with time points of the stewardship programme's main steps and actions

a clinical examination followed by an antibiogram was made mandatory before they were prescribed.

2.3 | Follow-up of the antimicrobial stewardship's impact

Three independent systems focusing on the different stages of antimicrobial usage (i.e. pharmaceutical sales, prescription and delivery, and administration) were used to document ASP impact on cephalosporin usage in the pig production sector (Figures 2 and 3). Since 1999, the pharmaceutical industry has reported yearly sales of veterinary medicinal products containing antimicrobials to the ANMV (the French agency for veterinary medicinal products). Using the proportion of sales by animal species provided by the marketing authorisation holder, pig exposure can be calculated and expressed as kg of live weight treated over the sum of the biomass produced and present, expressed in kg (derived from the amount of pigs slaughtered and sows present) to obtain a standardised figure for year-to-year comparison. Using additional information (Chauvin, 2010), the percentage of sows and growing pigs treated was also estimated (Meheust et al., 2017). Following on from the consensus, the specific monitoring tool for the prescribing and dispensing stage set up by veterinary practitioners recorded annual cephalosporin deliveries over the 2009–2012 period. Lastly, cephalosporin usage at farm level was documented by individual farm surveys initiated by INAPORC on a 3-year basis (Hemonic et al., 2018). The first and third of these tools were also able to detect any change in other antimicrobial classes.

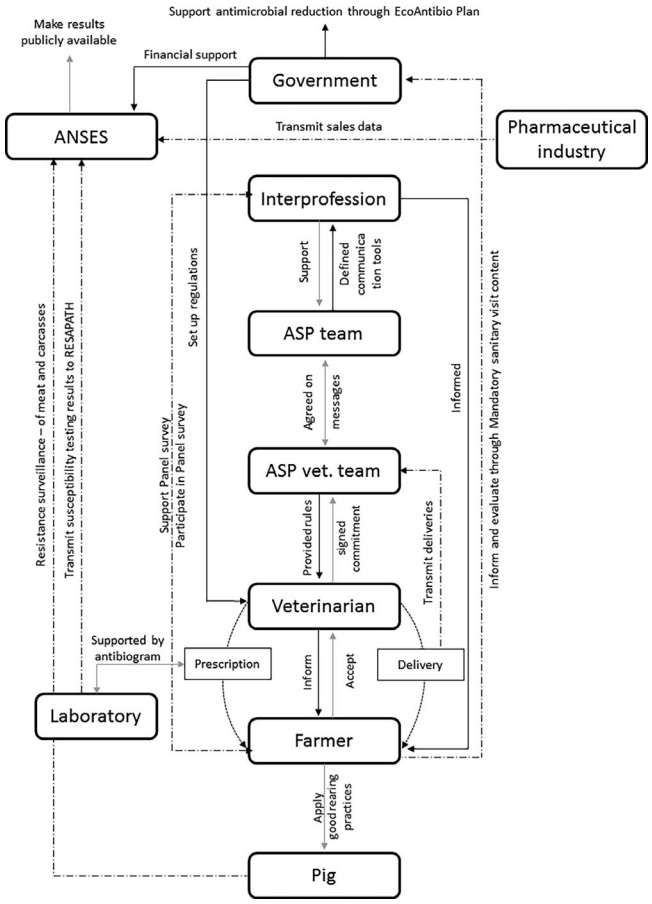

FIGURE 2 Players and actions of the cephalosporin stewardship programme implemented in French pig production (adapted from Dyar et al., 2017). Actions and behaviours are represented with black and grey arrows, feedback and follow-up information with dashed ones. ASP, antimicrobial stewardship programme; ANSES is the French Agency for Food, Environmental and Occupational Health & Safety

To document the impact of this ASP on antimicrobial resistance, data from two complementary tools already operational in France were used. RESAPATH, a voluntary surveillance system for antimicrobial resistance in pathogenic bacteria (RESAPATH, 2019), collects antibiogram results for clinical isolates from veterinary laboratories. The annual proportion of clinical *E. coli* isolates from pigs identified as non-susceptible to ceftiofur (i.e. displaying an inhibition zone diameter <21 mm for a 30 μg loaded disk) was calculated. In addition, since 2006, the annual surveillance of commensal bacteria at the slaughterhouse, performed in accordance with the European Union surveillance programme, includes the detection of cefotaxime microbiological resistance (by applying the epidemiological cut-off of 0.25 mg/L) in *E. coli* isolates randomly selected from the faecal content of about 170 randomly selected slaughtered pigs per year.

Clinical outcomes should also be monitored in order to assess the stewardship programme (McGregor & Furuno, 2014). The cephalosporin restrictions were not expected to worsen clinical outcomes, but in the light of the usage indicated by professionals, the mortality of suckling piglets could be an indirect indicator of a putative side effect of the restriction (Le Coz et al., 2012). Data were provided by the national technical monitoring system (IFIP, 2017).

To determine whether the ASP's implementation had a significant effect, indicators collected before (2006–2010) and after (2011–2017) the ASP were compared through percentages and means comparison tests. The correlation between usage data and resistance data was explored through a Spearman's rank correlation and odds ratio estimation.

3 | RESULTS

3.1 | ASP impact on cephalosporin usage in pig production

Consistently decreasing rates in cephalosporin usage were evident from the various monitoring systems and their different indicators (Figure 3). Firstly, 89 veterinarians (of 148 practitioners involved in pig production) signed and returned their consensus commitment form. Data on cephalosporin deliveries from 110 veterinarians (74.3% of all those contacted) were collected for the 2009–2012 period. A decrease in cephalosporins dispensed was of the same magnitude from 2010 to 2011 (−43%) and 2011 to 2012 (−45%), leading to an overall decrease of 68.9% between 2010 and 2012. The national monitoring

TABLE 1 Stewardship players, partners and related actions regarding cephalosporin usage in the French pig production sector (adapted from Dyar et al., 2017)

Players/partners	Actions and behaviour	Result/indicator
Farmers	• Take into account information received through the interprofessional mailing, production organisation newsletter, press and veterinary advice • Do not ask for cephalosporin • Apply all good rearing practices to prevent related diseases	% of using farms
Interprofessional stewardship team	• Agree on general and short-term objectives, a schedule, communication and follow-up tools	Communication tools harmonised
Interprofession	• Support the organisation of meetings • Communicate conclusions of the stewardship team to all interested bodies and farmers • Financially support detailed surveys on antimicrobial usage carried out by the French Pork and Pig Institute	Mailing INAPORC[a] panel results (on-farm usage)
Veterinary stewardship team	• Define, through veterinary consensus, rules for the prudent use of cephalosporins in pig medicine • Define, financially support and set up a follow-up system regarding cephalosporin deliveries	Clear rules published Amounts delivered
Veterinarians	• Follow recommendations: inform farmers, limit cephalosporin prescriptions according to the consensus rules and regulations • Sign a commitment to comply with the consensus and declare deliveries	Amounts delivered
Laboratories	• Apply good antibiogram practices • Transmit results to the RESAPATH[b] network	% non-susceptible isolates
ANSES	• Apply the European antimicrobial resistance surveillance protocol for National Reference Laboratory activities • Follow trends in sales of veterinary medicinal products containing cephalosporins through the activities of the French Agency for Veterinary Medicinal Products • Coordinate the RESAPATH network on antimicrobial resistance in pathogenic bacteria and publish results	% non-susceptible commensal (and zoonotic) isolates Quantities sold by manufacturers % non-susceptible pathogenic isolates
Government	• Financially support the activities of ANSES[c], the French agency in charge of food safety issues • Set-up regulations regarding critically important antimicrobials • Support antimicrobial reduction stewardship through National EcoAntibio Plans • Support professionals (farmers and veterinarians) awareness through mandatory sanitary visit content	Indicators on usage and resistance Publication of a Law, Decree and Order Definition of plans definition, financial support Questionnaire definition – technical support

[a]INAPORC, The French Interprofessional Pork Organisation.

[b]RESAPATH, Surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin.

[c]ANSES, French Agency for Food, Environmental and Occupational Health & Safety.

programme on sales showed a similarly marked decrease. Over 1 year, sales expressed as the amount of live weight treated (in animal course dose or ACDkg) related to the biomass produced and present (in kg) decreased by 51.8%. The estimated percentage of growing pigs treated decreased from 36.5% to less than 11% between 2010 and 2012, and the estimated percentage of treated sows decreased from 4.6% to 2.4%. The detailed farm surveys carried out in 2010 and 2013 confirmed both the decrease and differential exposure of production stages. The percentage of farms using cephalosporin at least once in sows decreased from 11% to 1%, in suckling piglets from 18% to 4%, in fatteners from 4% to 2% and in weaners it remained at 2%. The estimated figure for daily dose per pig produced decreased by a mean of 91% in sows and 98% in suckling piglets over the same period. None of the farms included in the sample survey in 2016 had used cephalosporin in weaners or fatteners. Similarly, according to the sales of veterinary medicinal products, a 98% decrease in pig exposure (in ACDkg/biomass) occurred between 2010 and 2017. A comparison of indicators before (2006–2010) and after (2011–2017) implementation of the voluntary measures systematically reveals a significant difference ($p < .01$).

3.2 | ASP impact on cephalosporin resistance

The data provided by resistance monitoring programmes on the non-susceptibility of *E. coli* to cephalosporins (Table 1, Figure 2) highlight benefits resulting from the decrease in usage (Figure 1). After an increase observed between 2000 and 2010, a statistically significant

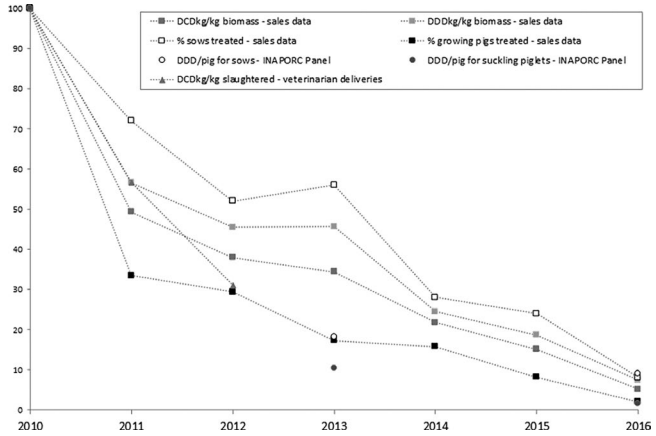

FIGURE 3 Decreasing trends in cephalosporin use in the French pig production sector from 2010 (baseline year: all indicator values set to 100) to 2016, measured by different systems (national sales data/ veterinarians' delivery records/the survey of a random sample of farms known as the INAPORC [The French Interprofessional Pork Organisation] Panel), using different indicators and for different animal categories

decrease in the occurrence of resistance to cephalosporins was noticeable in both clinical and commensal isolates.

A statistically significant positive correlation was found between the sales of cephalosporins during the previous year (expressed in ACDkg/biomass) and the occurrence of non-susceptibility to cephalosporin (expressed in per cent) in both clinical isolates ($r = 0.8$, $p = .0006$) and commensal isolates ($r = 0.7$, $p = .02$) (using a Spearman's rank correlation test). The odds ratio (for isolating a non-susceptible strain with an increase in use the previous year in ADDkg/biomass) was 3.12 [1.11–8.76] ($p = .03$) and 3.16 [1.7–5.86] ($p < .01$) for commensal and clinical isolates respectively.

3.3 | Adverse or side effects

A comparison of detailed data for 2010 and 2013 from INAPORC studies revealed neither a transient increase nor an upward trend in the usage of other antimicrobial classes for suckling piglets.

The data derived from the national technical monitoring system failed to show any increase in piglet mortality that could be related timewise to changes in cephalosporin usage. The survival rates assessed before (2006–2010) and after (2011–2015) the ASP did not show any statistically significant difference (both averages equalled 86.16%).

4 | DISCUSSION

The measures implemented first by professionals on a voluntary, consensual basis and subsequently enshrined in legislation were considered by the authors to be a relevant example of an ASP defined as "a coherent set of actions which promote using antimicrobials responsibly" (Dyar et al., 2017). The key factors considered as determinants of success were firstly the great awareness and deep involvement of all the national professional bodies concerned (representing veterinarians or farmers, pig production organisations, etc.). All these organisations shared common views and tools (such as mailing and articles in the professional journals). The stakes were clearly identified and understood, the good usage practices to be applied were clearly defined and communicated and the players' commitment was monitored and self-checked. The veterinarians involved were mainly specialised practitioners, of which there are a limited number (~150). Their strong commitment (illustrated by the high positive response rate to the signed commitment form and delivery data) demonstrated their collective support. This may have protected practitioners from individual farmers' insistent requests and competition between delivering structures (Bourély et al., 2018; Coyne et al., 2016; Hardefeldt et al., 2018). Pressure from farmers was probably limited by the timeliness and uniformity of information delivered by the whole professional farming environment: the same message was delivered by the interprofessional mailing, their veterinarian(s), production organisations and the press/journals. The timing also appeared to be important: support for decisions later promoted by authorities (through the national ecoAntibio Plan) was made easier because each step followed on from the previous one. When the new regulation on prescriptions came into force, prescription rules were not drastically modified as the circumstances under which critical antimicrobials could be used had previously been thoroughly revised by veterinarians. The huge success of the first voluntary step, without any reported adverse situations, made further steps possible. All the independent and complementary monitoring tools provided common and consistent positive feedback, highlighting the effectiveness of the ASP with a significant reduction in the use of cephalosporins, especially among the suckling piglets and sows targeted.

Positive feedback may also be given on the final impact on resistance either from a clinician's point of view (through clinical *E. coli* isolates) or a veterinary public health point of view (through commensal *E. coli* carried by healthy slaughtered swine). Both monitoring systems revealed a decrease in the percentage of non-susceptible strains, suggesting that the two objectives of the National EcoAntibio plan were fulfilled in this specific case, i.e. to preserve the efficiency of cephalosporins for pig health, and to reduce the contribution of usage among pigs to resistance. New data are now available regarding this last point, as a specific monitoring system was applied in the European Union in 2015 based on a selective medium containing cephalosporin to assess the presence of ESBL-producing *E. coli* on pig meat samples and in fattening swine caecal content samples (EFSA/ECDC, 2017). A greater prevalence of ESBL-carrying pigs was, therefore, estimated (34.7% in 2015, 28.1% in 2017) but prevalence in meat samples remained low (1.5% in 2015, 0.9% in 2017) and a downward trend is also perceptible.

The programme's successful impact on resistance has to be seen in relation to the strong tie thought to exist between animal exposure to cephalosporin and the carriage of resistant bacteria (Andersen et al., 2015; Cameron-Veas et al., 2015; Dohmen et al., 2017) despite a probable occurrence of the co-selection phenomenon (Cameron-Veas et al., 2015; Lucas et al., 2018).

To assess the clinical impact of the reduction in cephalosporin use on pig health, suckling piglet mortality might not be the best indicator because locomotor disorders (the main reason for treating suckling piglets with cephalosporin in France in 2010 [Hemonic et al., 2014]) do not always lead to death. It is also worth noting that, the detailed data provided by the INAPORC studies showed no increase in the usage of antimicrobials from any other class for suckling piglets (Hemonic et al., 2018). It may have been easier to obtain and maintain support for the restriction on cephalosporins because no strong direct impact impaired animal health and welfare, as reported by French veterinarians (Bourély et al., 2018).

The stewardship programme could only be evaluated in a before–after perspective as measures were adopted and applied on a national basis. It can only be speculated from other countries' reports that without any professional and regulatory initiatives, use among suckling piglets in particular would have been maintained at the very least, and possibly even increased (Schaekel et al., 2017).

In France, the evaluation of the cephalosporin stewardship programme in the pig production sector will be supplemented by an assessment of pig farmers' knowledge and their degree of awareness regarding the use of critical antimicrobials for pigs. This assessment will take place in the coming 2 years through the mandatory sanitary visit carried out by veterinarians and its associated formal questioning of farmers, which will focus on antimicrobial resistance (Ministry of Agriculture & Food, 2018).

All of the seven basic requirements of an ASP listed by Turnidge (2015) were fulfilled: (a) the executive ownership was indeed owned at the highest levels of the pig production sector; (b) agreed prescribing guidelines were defined by an ad hoc group of practitioners; (c) access to third- and fourth-generation cephalosporins was later restricted by law; (d) change was driven maybe less by local champions than by broadly representative teams; (e) inappropriate prescriptions were prevented firstly by consensus and secondly by regulations; (f) the measurement of usage, audits and feedback was efficient and complete and (g) access to cumulative resistance data was supported by RESAPATH and mandatory surveillance activities. As underlined by Turnidge (2015), ASPs in a food production sector has to be a cooperative venture among regulators and all professionals.

In a broader perspective, this first stewardship programme opened the door to a broad reflection on antimicrobial use in the pig sector that was supported by the tools implemented for the purpose, such as the regular on-farm survey (Hemonic et al., 2018). This successful mobilisation for a responsible and prudent use certainly also benefitted the initiatives for other species and the national momentum enforced by EcoAntibio plans (Ministry of Agriculture Agro-Food & Forestry, 2016).

5 | CONCLUSION

This description and analysis of the ASP adopted by the French pig production sector regarding cephalosporin usage showed that it could rapidly have a successful impact on reducing usage and containing resistance. All attempts to circumvent measures (e.g. pressure from farmers) and all particularities (e.g. the potential for competition between prescribers) were considered and overcome through a clear definition of usage restriction rules, the widespread involvement of all parties and rapid positive feedback provided by complementary ad hoc tools covering both usage and resistance.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Fabien Verliat: Conceptualization; Writing-review & editing. **Anne Hémonic:** Conceptualization; Data curation; Writing-review & editing. **Sylvie Chouet:** Conceptualization; Writing-review & editing. **Philippe Le Coz:** Conceptualization; Writing-review & editing. **Mélanie Liber:** Conceptualization; Writing-review & editing. **Eric Jouy:** Data curation; Writing-review & editing. **Agnès Perrin-Guyomard:** Data curation; Writing-review & editing. **Anne Chevance:** Data curation; Writing-review & editing. **Didier Delzescaux:** Conceptualization; Writing-review & editing. **Claire Chauvin:** Formal analysis; Investigation; Visualization; Writing-original draft; Writing-review & editing.

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