Drug hypersensitivity in cattle

An account of how a signal is processed in veterinary pharmacovigilance

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There was an increase in the frequency of reported cases of immediate drug hypersensitivity in cattle, observed first in France and then more generally in the European Union between 2020 and 2023, leading to coordinated management of this signal at European level. The main hypothesis was that the cattle were sensitised to povidone, an excipient contained in many veterinary medicines, particularly vaccines. Although the assumed mechanism could not be confirmed, risk management measures were taken, including the exclusion of povidone from the manufacturing processes of certain vaccines. By 2024, the frequency of hypersensitivity reactions observed in cattle had returned to its previous level.

A RARE BUT WELL-KNOWN ADVERSE EFFECT IN CATTLE

Immediate (or Type 1) hypersensitivity reactions are a recognised phenomenon described in many animal species, including cattle. Symptoms include respiratory problems, oedema, cyanosis and sometimes shock, which can lead to the death of the animal. Certain classes of drugs, such as antibiotics and vaccines, are among the possible causes of these hypersensitivity reactions. They are mentioned as a potential adverse effect in the package leaflets of many medicines.

Hypersensitivity reactions in cattle following the administration of various medicines have regularly been reported to the French Agency for Veterinary Medicinal Products (ANMV), part of ANSES. However, this type of reaction is considered to be very rare (fewer than one animal in 10,000 treated) and the reported cases tend to be isolated.

EMERGENCE OF THE SIGNAL IN FRANCE

In 2020, thanks to adverse effect reporting by veterinarians, the ANMV detected clusters of immediate hypersensitivity reactions in cattle, triggered mainly by antibiotic injections. These grouped hypersensitivity reactions (several animals reacting simultaneously or within a short period of time) occurred on farms following the administration of antibiotics with a long history of use, without any such clusters previously being observed. In 2020, the number of cases was still limited, with 16 recorded. However, they had been reported by several veterinarians and seemed to occur mainly on farms on which a new vaccine against bovine mastitis had been administered.

Investigations carried out on the products triggering these reactions had not identified any "batch effect" or change in the manufacturing processes. This led to suspicions that the animals had been sensitised by an external factor, whether environmental or medicinal. An ANMV survey of reporting veterinarians found no major differences in the practices of affected farms compared with control farms (farms monitored by the same veterinarians, but not affected by these reactions).

However, previous vaccination against mammary infections was identified in around 50% of the farms concerned, compared with 21% of control farms [1].

EXTENSION OF THE SIGNAL TO EUROPEAN LEVEL

In the years that followed, this signal was extended both geographically and clinically: a European-level analysis of veterinary pharmacovigilance data showed an overall increase in the frequency of hypersensitivity reactions in cattle (clusters as well as isolated cases) to various types of medicines (antibiotics as well as vaccines, anti-inflammatories, antiparasitics, mineral supplements, etc.) in several other European countries (mainly Spain, Italy and Belgium).

While various medicines were mentioned in the medical histories of the animals concerned, the product most frequently cited in the declarations was a vaccine against bluetongue, a disease affecting all domestic ruminants. Prior administration of this vaccine was reported in almost 25% of the cases of bovine hypersensitivity recorded in France in 2022. The profile of the animals affected by hypersensitivity reactions had also changed, from mainly dairy cattle (75% of cases recorded in France before 2022) to mainly beef breeds (67% of reports in France between 2022 and early 2023).

INVESTIGATIONS COORDINATED BY EMA

Faced with the increase in these pharmacovigilance reports, beginning in 2023, the European Medicines Agency (EMA) organised coordinated management of this pharmacovigilance signal at European level, bringing together experts from several veterinary medicine agencies in Europe (including the ANMV) along with the pharmaceutical companies concerned, in an attempt to gain a better understanding of the mechanisms involved.

The variety of medicinal products triggering these reactions and the frequency of certain vaccinations in the medical histories of the affected animals supported the hypothesis of prior sensitisation of cattle through vaccination. In the absence of any other identified lead and insofar as most of the reported reactions had been triggered by the administration of medicines containing povidone (an excipient[1] found in numerous veterinary medicines), the hypothesis of prior sensitisation to this substance was explored as a priority, especially since a similar phenomenon had already been reported in the literature in the mid-1990s [2].

Additional studies to explore this hypothesis were then carried out by the manufacturers concerned under the coordination of the EMA. The findings did not confirm the involvement of povidone or the link with prior ad-

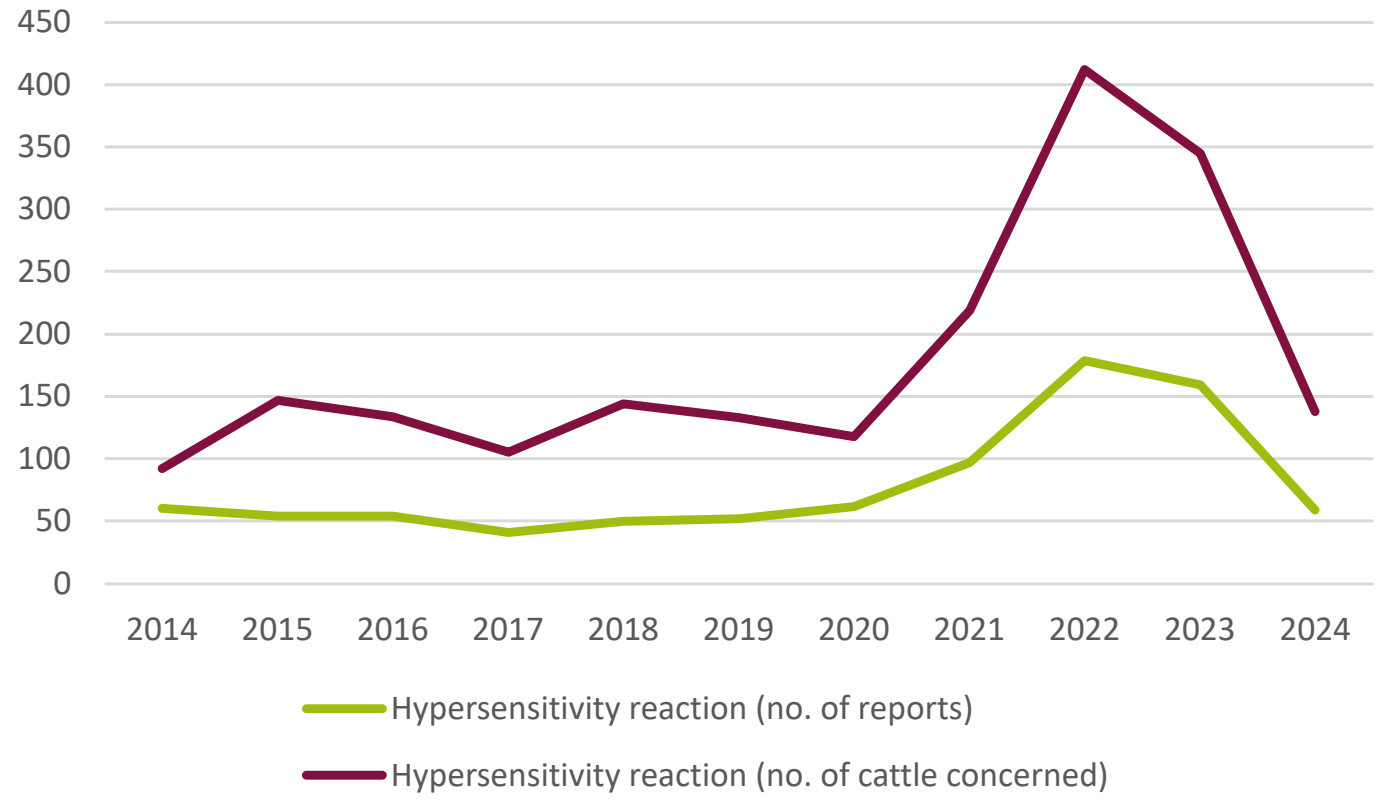

Figure 1 - Annual trend in hypersensitivity reactions in cattle reported to the pharmacovigilance scheme in France.

ministration of the main vaccines in question. However, measures were taken by the pharmaceutical industry from 2023 to limit the risk of sensitisation to povidone, by removing this substance from the manufacturing process of certain vaccines. This is because although povidone was not used directly in these vaccines, it was used in the industrial manufacturing process and could therefore have ended up in trace amounts in the finished product.

IMPACT OF THE MEASURES TAKEN

A decline in the number of reports of bovine hypersensitivity reactions has been observed since 2023, with the level in 2024 being similar to that prior to 2020 (Figure 1), corresponding to a normal frequency of reactions for the medicines concerned.

At this stage, it is difficult to determine whether this return to normal is due to the changes made to certain vaccines or to an adaptation of practices in the field, such as the use of medicines that do not contain povidone or a change in vaccination practices. On several occasions since 2022, the ANMV has issued communications about this signal to veterinarians, which could potentially have influenced the use of the medicines concerned [1,3].

In any case, given that risk management measures have been taken by industry and a favourable trend has been observed, the specific signal management procedure put in place by the EMA came to an end in late 2024. There are no plans to continue investigations or take any further action in relation to this signal [4]. However, manufacturers and the veterinary medicine authorities are continuing to closely monitor reported cases of bovine hypersensitivity, so that they can respond in the event of a new alert. In this context, it is important for veterinarians to maintain vigilance and report any adverse effects they observe to pharmacovigilance.

The detection and investigation of this signal led to the identification of a new risk inherent in the use of vaccines in animals. Discussions are under way at European level to take better account of this risk of sensitisation to povidone in the manufacturing process for veterinary vaccines.

Jacques BIETRIX, Elisabeth BEGON, Flore DEMAY, Grégory VERDIER (French Agency for Veterinary Medicinal Products, ANSES)

TO REPORT AN ADVERSE EFFECT TO VETERINARY PHARMACOVIGILANCE

→ **National veterinary pharmacovigilance scheme**

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[1] Begon E, Demay F, Laurentie S. Réactions d'hypersensibilité immédiate à des médicaments chez les bovins : quelles nouveautés en 2022/2023 ? SNGTV [Internet]. juill 2023 [cité 30 janv 2025];(Numéro spécial). Disponible sur https://anses.hal.science/anses-04409010v1

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[3] Piquemal C, Begon E, Demay F, Laurentie S. Cas groupés de réactions d'hypersensibilité de type 1 chez des bovins suite à l'administration d'antibiotiques : point sur la situation en décembre 2021. [Clustered cases of type 1 hypersensitivity reactions in cattle following the administration of antibiotics: update on the situation in December 2021]. La Dépêche Vétérinaire [Internet]. Feb 2022 [cited 30 Jan 2025];(1606). Available on https://hal-anses.archives-ouvertes.fr/anses-03726413

[4] Signal management (veterinary medicines) | European Medicines Agency (EMA) [Internet]. 2023 [cité 30 janv 2025]. Available on https://www.ema.europa.eu/en/veterinary-regulatory-overview/post-authorisation-veterinary-medicines/pharmacovigilance-veterinary-medicines/signal-management-veterinary-medicines

[1] Component of a medicinal product, other than the active substance or the packaging materials, which does not confer any therapeutic or preventive properties, but may play a role particularly in the absorption (assimilation) and stability of the medicinal product, and affects its appearance, colour and taste.