Syndromic surveillance: applying big data to vigilance

What is it for?

The aim of a health vigilance scheme such as toxicovigilance is to detect signals which, if validated, will trigger immediate actions and measures to correct a situation where there is a risk of human poisoning and prevent similar new episodes (information, investigation, withdrawal of a consumer product, etc.).

These signals can come from different complementary sources that are either qualitative ("spontaneous" reporting, scientific monitoring) or quantitative (statistical analysis). First of all, healthcare professionals can notify the competent authorities of situations they consider abnormal. As part of their toxicovigilance mission, the eight poison control centres (PCCs), each covering a part of the country, report to ANSES any unusual, serious and/or avoidable cases of poisoning of which they become aware. However, for any given PCC, identification of these cases, although exhaustive and objective, is based on an assessment of "only" those cases of which it has been informed, and does not by definition allow for any comparison with cases of which the PCC is unaware. A single PCC does not necessarily have the means to detect a possible link between poisoning cases with shared characteristics (exposure agent, circumstances, severity, symptoms, etc.) in different parts of the country. On the other hand, this "diffuse" signal can be more easily detected by statistically analysing the Poison control centres' national database (SICAP), where the data from all the PCCs are gathered, , especially since these data are numerous and go back such a long way in time, enabling statistical comparisons.

This is why the challenge for vigilance in recent years has been to develop automated signal detection methods based on statistical algorithms, which analyse large health databases in search of an "unusual event" that could pose a risk to the population [1,2]. In early 2018, in conjunction with Inserm[1] and the PCC network, ANSES set up an automated toxicovigilance signal detection programme based on SICAP data, one of whose components concerns "syndromic surveillance".

How does it work?

In toxicovigilance, syndromic surveillance is based on the systematic analysis in "real time" (or quasi-real time) of poisoning cases recorded by the PCCs in SICAP, with the aim of detecting unusual peaks of cases, compared to what has been observed in the past, which then correspond to a "statistical" signal.

In particular, the analysis focuses on "medical entities" (or syndromes), which are defined as a group of clinical signs or symptoms, each of which can be used independently for coding SICAP poisoning cases. These entities correspond to an affected organ, function or system of the human body (cardiac rhythm disorders, skin rash, irritation of the upper airways, consciousness disorders, "anticholinergic eye", etc.), without any prior knowledge of the agents that may be responsible for their occurrence. Initially designed to detect the health consequences of acts of bioterrorism, syndromic surveillance should help identify cases of poisoning with similar clinical evidence, spread unevenly across the country, without prior knowledge of whether the subjects were exposed to the same agent or the same family of agents. Syndromic surveillance aims to identify both accidental exposure and malicious acts.

A total of 66 medical entities were predefined with the help of PCC expert toxicologists, and then tested. In practice, monitoring a syndrome means monitoring poisoning cases in SICAP that include at least one of this entity's clinical signs.

For each of the medical entities, a statistical query performs a daily comparison (on day D) of the number of cases observed over the last seven days (from D-1 to D-7) with the "average number" of cases observed successively during previous weeks (from D-14 to D-21, from D-22 to D-29, etc.), including the entire history of SICAP data going back almost 20 years. The algorithm detects a statistical signal when the number of cases observed is higher than expected. Any possible seasonality of the poisoning cases of the monitored medical entity and the overall activity of the PCCs, which may change over time, are all taken into account by the statistical model.

1. Inserm: National Institute of Health and Medical Research

Statistical analysis does not, and is not intended to, establish an actual link between poisoning cases of the same signal. In the event of a signal, the toxicologists from ANSES and the PCCs review the medical records of the poisoning cases making up the signal, using the forms available in the SICAP, and validate or rule out the signal. If the poisoning cases are linked (= seem to be caused by the same agent, even if unidentified), the signal is validated, which enables a possible risk for the population to be confirmed and characterised. If the poisonings are not related to each other (e.g. different agents), the signal is ruled out.

What are some specific examples?

This scheme was introduced in April 2018. An initial analysis of syndromic surveillance showed that out of 20 statistical signals detected between April and December 2018, the majority (16 signals) corresponded to a chance association of cases, without any link between them (situations having no common points, notably regarding the agent). These signals were not validated ("false positives"). This initial assessment led to certain medical entity definitions being modified, by refining their detection criteria. For example, for analysis of the "visual acuity disorders" entity, cases exposed by the ocular route were ruled out in order to exclude vision disorders due to eye splashes, which are usually of very diverse origin.

However, four signals were validated and led to health alerts being issued.

On 26 April 2018, analysis of the 255 cases in the "rash" medical entity signal[2] identified 28 cases due to snake bites, showing an earlier occurrence of viper poisonings for the season. The alert was given in the context of stock shortages of viper anti-venom, which had been recurring since 2016.

On 31 July 2018, surveillance of the "anticholinergic eye[3]" entity detected a signal consisting of 31 cases, including six clustered cases, of people who had consumed jimsonweed leaves (*Datura stramonium*) [3] sold in a market in place of spinach leaves. The seller was not identified.

On 30 October 2018, a signal consisting of 25 cases, also of the "anticholinergic eye" entity (Figure 1), revealed collective food poisoning on Reunion Island of six people who thought they had collected edible leaves, which were in fact jimsonweed leaves.

Lastly, on 20 November 2018, a signal concerning two cases of the "anticholinergic syndrome" entity (Figure 1) was the starting point for an alert due to organic buckwheat flour contaminated with jimsonweed and sold in supermarkets. These cases concerned two people poisoned during a meal on 17 November, after having eaten home-made pancakes prepared with a bag of flour purchased in a supermarket.

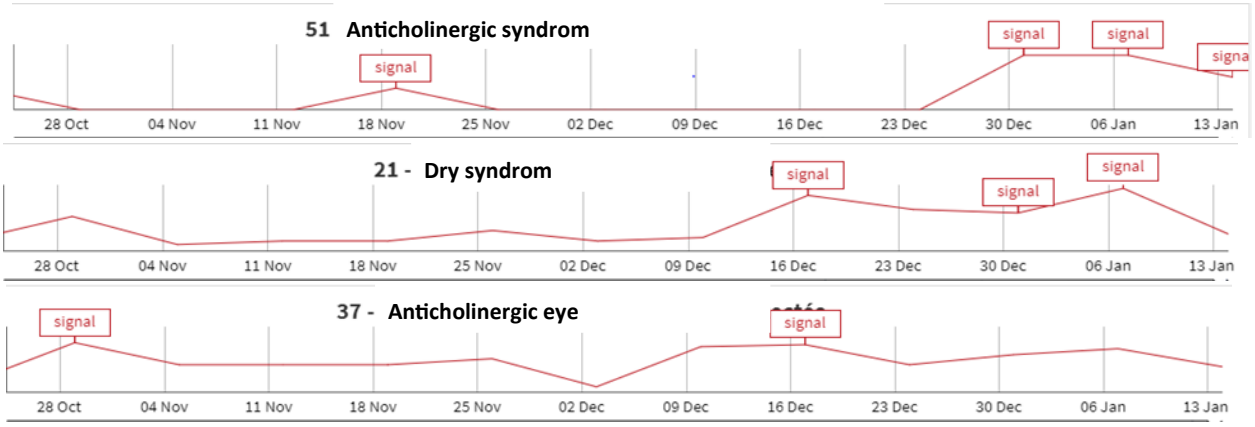

Figure 1: Change over time in the "anticholinergic syndrome", "dry syndrome" and "anticholinergic eye" medical entities monitored in syndromic surveillance. Source: R Connect®, ANSES.

2.This entity includes signs of skin irritation, redness, oedema, burning, etc.
3.This entity consists of signs of pupil dilation, decreased visual acuity, dry eyes, etc.

In addition to the syndromic surveillance, the search for similar cases in SICAP then identified a second episode of collective poisoning of four people who, also on 17 November, had presented with anticholinergic signs after consuming homemade pancakes made with a bag of flour of the same brand and from the same supplier, but purchased in a supermarket in a different region.

Following this alert and the traceability investigation with the producer that marketed the flour, on 23 November the DGCCRF[4] asked the interdepartmental directorates located near the hypermarkets and supermarkets concerned to take steps, without delay, to withdraw and recall the contaminated batch of flour, in order to prevent the risk of new poisoning cases [4].

However, on 14 December 2018, a signal consisting of 11 cases of the "dry syndrome[5]" entity (Figure 1) identified four further cases of poisoning with the buckwheat flour responsible for the alert (same brand and batch number), but in which the bags had been purchased on 8 December, after the first management measures had been introduced. Four days later (18 December), a new signal for this entity identified six further cases of poisoning by the same flour, this time bought on 15 December in another shop. ANSES alerted the DGCCRF to the developments in the situation and new measures to withdraw/recall contaminated products were taken [3]. Three new cases, involving flour purchased on 5 January 2019, were detected on 12 January ("anticholinergic syndrome", Figure 1). In total, as of 15 January 2019, 73 cases of poisoning in 23 different medical files[6] had been identified (Figure 2).

What is the outlook?

Syndromic surveillance is a useful tool for the early detection of weak health signals. Developed for toxicovigilance less than a year ago, it has helped with the prompt identification of several signals.

Other methods of automated signal detection are being developed using PCC data.

Studying chronological trends in exposure cases associated with certain families of agents makes it possible to detect progressive increases in these poisonings, not through "epidemic" peaks in cases, which are more easily detected in the short term, but through medium-term increases.

Lastly, the automated search for new, unknown and/or abnormally frequent associations between certain characteristics of poisoning cases and agents (symptoms, substances in the products, exposure circumstances, etc.), known as non-targeted data mining, is another automatic detection method that can reveal weak signals.

Together with the continuation of active reporting schemes, this work represents one of the tools for future toxicovigilance.

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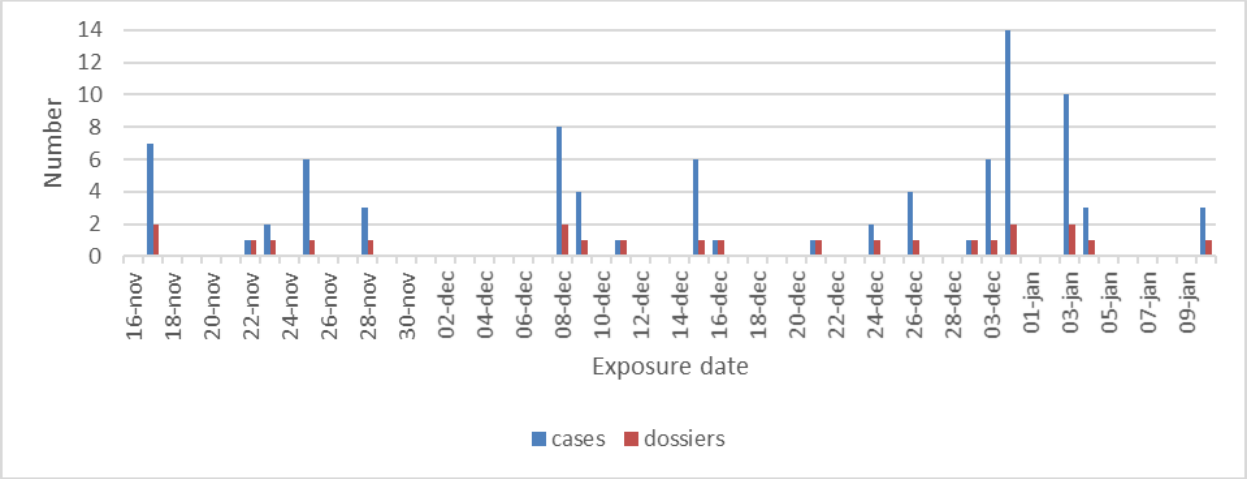

Figure 2: Distribution of exposures to buckwheat flour contaminated with jimsonweed (*Datura stramonium*), recorded by the PCCs since the beginning of the alert (number of cases and medical files – a medical file includes all cases of people having consumed the same meal).

4.DGCCRF: Directorate General for Competition, Consumer Affairs and Fraud Control.
5.An entity consisting of signs of dryness of the mucous membranes, including dry eye syndrome (or anticholinergic eye).
6.Each medical file contains either a single case or collective cases for people who shared the same meal.

References

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