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Size rules life, but does it in the assessment of medical vigilance best practice? Towards a testable hypothesis

Laurent Seuront [a,*], Dorine Seuront-Scheffbuch [b]

[a] CNRS, Univ. Lille, Univ. Littoral Côte d'Opale, UMR 8187, LOG, Laboratoire d'Océanologie et de Géosciences, F 62930 Wimereux, France
[b] Agence Régionale de Santé (ARS) de Picardie, 52 rue Daire, CS 73706, 80037 Amiens Cedex 1, France

HIGHLIGHTS

- We infer the applicability of scaling concepts to haemovigilance.
- Haemovigilance is based on the occurrence of serious adverse reactions and events (SARE) following blood transfusion (BT).
- SARE is essentially a power-law function of BT.
- We show the existence of two power-laws depending on BT.
- Beyond a critical threshold of BT, the safety of the transfusion process is increased.

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ABSTRACT

The goal of this paper is to infer the applicability of scaling concepts to haemovigilance based on the study of the relationship between severe adverse reactions and events (SARE) and blood transfusions (BT). We hypothesize that in a haemovigilance operating optimally, SARE should be a power-law function of BT as SARE $= \alpha BT^{\beta}$. We investigated the relationship between yearly BT and the related SARE reported in 12 French hospitals of the Picardie State from 2004 to 2015. First we found that when integrated over the whole period 2004–2015, SARE were significantly described by a power-law function SARE $\propto BT^{1.51}$ for 10 of the 12 hospitals considered. The numbers of SARE in these two hospitals is drastically over-estimated by this power-law, that is 1.9- to 4.3-fold lower than those predicted by the power-law. When considered on a yearly basis, we consistently found that SARE was also significantly described by a power-law function of the form SARE $\propto BT^{1.44}$ for 10 of the 12 hospitals considered. In turn, the occurrence of SARE in the two other hospitals was strongly over-estimated by this power-law, though it is also significantly described by another power-law, SARE $\propto BT^{1.11}$. We specified these results through separate yearly analyses and found the relationship between SARE and BT was best described by a power-law with $\beta = 0.90$ in 2004, a linear relationship from 2005 to 2007 and a power-law with β ranging from 1.49 and 1.92 from 2008 to 2014. Finally, in 2015, the relationship between SARE and BT was significantly described by a power-law SARE $\propto BT^{1.17}$ for the 12 hospitals considered. Overall, our results suggest that hospitals performing more blood transfusions are more efficient as the observed negative effects of blood transfusions increase relatively slower than in hospitals performing less transfusions.

* Corresponding author.
E-mail address: laurent.seuront@cnrs.fr (L. Seuront).

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1. Introduction

Over the last decades, it has become increasingly and mesmerizingly evident that the growth of the multiple networks that sustain life, from intracellular to cardio-vascular patterns, but also from anthills and beehives, to cities, economies and companies can be expressed as simple '*universal mathematical laws*', fundamentally stating that doubling in size requires only 80–85% increase in infrastructure and energy consumption [1–3]. These laws find their roots in the early work of Otto Snell in 1892 on the allometric dependence of brain weight on body weight and mental abilities [4]. The term allometry was later formalized [5,6] as a conventional designation in biology of the phenomena of differential growth of organs, tissues and activity.

One of the most fundamental allometric scaling laws, introduced by Max Kleiber in 1932, relates how basal metabolic rate r of endothermic vertebrates (birds and mammals) changes with body mass M as $r \propto M^{3/4}$ [7]. A striking consequence of Kleiber's law is that a horse may be 10,000 times heavier than a mouse, it only consumes 1000 times more energy (*i.e.* $10{,}000^{3/4} = 1000$). It is then more efficient to be larger as smaller animals are less energy efficient. Noticeably the same phenomenon holds from the cellular to the population level. More generally, there is now compelling evidence that despite spanning more than 21 orders of magnitude in size from microbes to whales, living organisms obey a host of remarkably simple and systematic empirical scaling laws that dictate how biological quantities such as metabolic rate, time scales (*e.g.* cardiac dynamics and locomotion), and weights and shapes of component parts change with size [8–11]. The mesmerizing universality of these laws is telling us something essential about the way life is organized and the constraints under which it has evolved.

More fundamentally, the existence of a power-law between two quantities is the results of the interplay between a range of internal and external conflicting forces that converge towards an optimization of performance. For instance, one of the first models accounting for the scaling variant behavior in cardiac dynamics, demonstrates that competing/conflicting inputs of the sympathetic (increasing heart rate) and parasympathetic (decreasing heart rate) systems with non-linear feedback are key to emerging dynamics characterized by power-laws [12]. This is the reason why both mammal and plant vascular systems obey the same scaling law [1] as they both fulfill the same function, *i.e.* transporting a fluid in a ramified network against gravity. Scaling laws can, however, exhibit lower and upper limits. For instance, Newton's Universal Law of Gravitation put an upper limit to the size of animals, which is fundamentally restricted by both the mechanical strength of bone and the mass of the Earth [9,13]. In other words, an elephant could not fly and a whale could not walk even if they respectively had wings and legs. Similarly, the smallest size of capillary vessel is dictated by both the size of the single layer of rolled-up endothelial cells forming the vessel and the size of the maximally deforming erythrocyte to pass though. Scaling laws also appear to obey another principle called symmorphosis, or economy of design [14]. This principle lies on the idea that biological structures and functions are designed so as to meet but not exceed the maximal demand. As a consequence, the design which confers the highest fitness provides for the maximum demand [15]. This principle further implies that any significant deviation of an individual or species from the value predicted from a scaling law indicates a sub-optimal and often pathological design, which implies a substantial fitness cost (*e.g.* acromegalic gigantism and excessive obesity), or a special adaptive response to selective pressures not operating on the other organisms or individuals used to derive the equation [16,17]. A typical example of these transitions is provided by the dependence of the exponents which define power-laws in physiologic dynamics (sleep stage and arousal transitions) to metabolic rate and body mass; see [18], their Fig. 4. The principles discussed above apply to a range of complex systems (*e.g.* medicine, individual and collective behaviors, species diversity, evolution, palaeontology, economics, sociology, linguistics, sports, and various areas of physics and chemistry) where fitness or more generally some performance criterion is optimized. For instance, proxies of city energy usage, such as number of gas stations and length of electric cables, scale sub-linearly with the size of a city, indicating that people living in bigger cities are more energy-efficient. As such scaling laws have been suggested as a design principle, as a scaling design is structurally and functionally efficient as it requires little energy to sustain itself [2,19–21]. More specifically, a remarkable review [22] poses the fundamental question: "*Do biological phenomena obey underlying universal laws of life that can be mathematized so that biology can be formulated as a predictive, quantitative science?*" and further offers scaling as an exemplar of such universal behavior in biological sciences. In that regards, it is remarkable that in the context of human physiology, diverse organ systems that operate over various ranges of time scales (e.g. heart rate fluctuations, respiratory inter-breath intervals, gait dynamics, wrist motion, brain dynamics of arousals during sleep) all exhibit scaling laws with similar exponents that are close to unity [23–28].

However, despite the plethora of medical literature showing modification and loss of scaling properties under various clinical conditions (*i.e.* stress, age, parasitism, disease; [29,30]), so far no attempt has been made to apply scaling concepts in the context of medical vigilance, *i.e.* the set of organized surveillance procedures related to adverse or unexpected reactions in patients following a medical procedure, and devoted to prevent their occurrence and recurrence. By analogy with the various systems discussed above where the interplay between various (internal and external) forces leads to power-laws, the number of reported adverse transfusion events is impacted by different, and potentially conflicting, forces. First, the resources (both funding and staff) allocated to hospitals to prevent such events (i.e. to reduce what would be the natural frequency of adverse events if those precautions were not in place), hence the effectiveness of the medical vigilance varies between hospitals. Second, it is well established that many adverse events are either un-noticed, un-recognized, or un-reported, which further perturbs the observed occurrence rate. The identification of a power-law signature in a vigilance process may, however, be considered as a sign of robustness by analogy with the power-law behaviors exhibited by a range

of biological and physical systems, where they are considered as adaptive because they serve as an organizing principle for highly complex, nonlinear processes, avoid restricting a functional response to highly periodic behavior, and are also an indication of error tolerance, as they allow to cope with stress and unpredictable environments [31]. In this context, the main goal of this study is first to assess the applicability of scaling concepts in medical vigilance based on original data from the field of haemovigilance, and second to discuss how power-law behaviors could be used as an objective and quantitative tool assessment tools in the evaluation of vigilance processes.

2. Power-laws and medical vigilance: a testable hypothesis

2.1. The hypothesis

Based on the aforementioned arguments, we hypothesis that the number n of severe adverse reactions and events reported in different hospitals following the administration of a pharmaceutical product, the use of a medical device or any specific medical procedure, should be a power-law function of the number N of administered pharmaceutical products, medical devices used or surgery performed. The presence of a power-law, $n = \alpha N^{\beta}$, would then indicate the presence of a system performing optimally. In turn, hospital falling outside the prediction of the power-law may function sub-optimally or respond to different pressures not operating on other ones. More specifically, it can further be suggested that vigilance systems characterized by scaling exponents $\beta < 1$ and $\beta > 1$ would indicate processes where the number of severe adverse reactions and events respectively grow slower and faster than N. For instance, doubling N in a context where $n = \alpha N^{0.75}$ and $n = \alpha N^{1.5}$ would result in $2^{0.75} = 1.68$-fold (i.e. 68%) and $2^{1.5} = 2.18$-fold increase (i.e. 118%) in the related amount n of severe adverse reactions and events. The former case would then characterize a system that is pharmaceutically or medically safer than the latter. This issue is critical as it is at the core of the much needed identification of objective and quantitative assessment tools in the evaluation of vigilance processes [32].

2.2. Haemovigilance as a case study

A first step towards the validation of our hypothesis is made using the process of haemovigilance, where the assessment of the safety of transfusion services and practices is based on the ratio between the number of blood transfusions (BT) performed and the related severe adverse reactions and events (SARE) [33–36]. Specifically, haemovigilance is defined as a set of surveillance procedures covering the whole transfusion chain from the collection of blood and its components to the follow up of its recipients, intended to collect and access information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence and recurrence [37]. The ultimate goal of a haemovigilance system is to improve the safety of blood transfusion [38]. Specifically, in France, the reporting of adverse transfusion reactions has been mandatory since 1994 [39], according to previously described rules [40,41], and includes all severity levels of transfusion reaction as well as all degrees of imputability to the transfusion. Specifically, in each public or private hospital performing blood transfusion, a physician (referred hereafter to as haemovigilance correspondent) is in charge of haemovigilance reporting and ensures compliance with blood transfusion regulations. Following a transfusion reaction, the haemovigilance correspondent of the Etablissement de Transfusion Sanguine (ETS) or of the blood service (Etablissement Français du Sang, EFS) – the public organism performing pre-transfusion blood testing and cross-matching before blood products are delivered to hospitals – coordinates the necessary additional investigations. All SARE are systematically reported through a purpose-designed national digital reporting system (e-fit) developed by the French Health Products Safety Agency (Agence française de sécurité sanitaire des produits de santé), which became the French National Agency for Medicines and Health Products Safety (Agence nationale de sécurité du médicament, ANSM) in 2012. The details of the haemovigilance report are validated at the state level by the haemovigilance state coordinator (Coordinateur Régional d'Hémovigilance et de Sécurité Transfusionnelle, CRHST) of the state health agency (Agence Régionale de Santé, ARS).

The relationship between SARE and BT has, however, still not been quantified in the medical literature in general and in the transfusion-related literature in particular despite the growing number of haemovigilance programs around the world over the last 20 years [42–45]. Specifically, we investigated the potential relationship between BT and the related SARE reported in 12 French hospitals of the Picardie State from 2004 to 2015 (Table 1). To assess whether the relationship between BT and SARE was best fitted by a linear, power-law, logarithmic, or an exponential function, we used the theory of model selection based on Akaike's information criterion (AIC) [46].

First, we investigated the relationship between the total numbers of blood transfusions performed over the whole period 2004–2015 ($BT_{2004–2015}$) and the related severe adverse reactions and events ($SARE_{2004–2015}$). We found that $SARE_{2004–2015}$ was consistently significantly ($p < 0.01$) described by a power-law function of the form $SARE_{2004–2015} \propto (BT_{2004–2015})^{1.53}$ for 10 of the 12 hospitals considered (Fig. 1). This result implies that doubling the amount of blood transfusions performed in these hospitals leads to 189% increase in the related severe adverse reactions and events, suggesting that the negative effects of blood transfusion increase faster that the amount of transfusion performed. In turn, the number of SARE observed in two hospitals (Amiens and Saint Quentin) is drastically over-estimated by this power-law; the observed $SARE_{2004–2015}$ in Amiens ($SARE_{2004–2015} = 552$) and Saint Quentin ($SARE_{2004–2015} = 143$) are respectively 1.9- and 4.3-fold lower than those predicted by the power-law, *i.e.* 2360 in Amiens and 267 in Saint Quentin. These results suggest that hospitals performing more blood transfusions are relatively more efficient as the observed negative effects of blood transfusions seem to increase

Table 1
List of the hospitals considered in the present work, together with the minimum (Min) and maximum (Max) amount of blood transfusions (BT) they performed from 2004 to 2015, and the subsequent severe and adverse reaction events (SARE).

Hospitals	BT		SARE	
	Min	Max	Min	Max
Abbeville	2486	3554	5	13
Amiens	16146	28949	26	77
Beauvais	3896	5600	15	31
Château-Thierry	741	1913	0	4
Chauny	670	1077	0	5
Compiègne	3331	5854	7	29
Creil	2900	6000	13	22
Laon	1430	2016	0	8
Senlis	1643	2229	3	11
Soissons	2443	3443	5	17
St. Come	1105	1778	1	4
St. Quentin	4456	8479	3	23

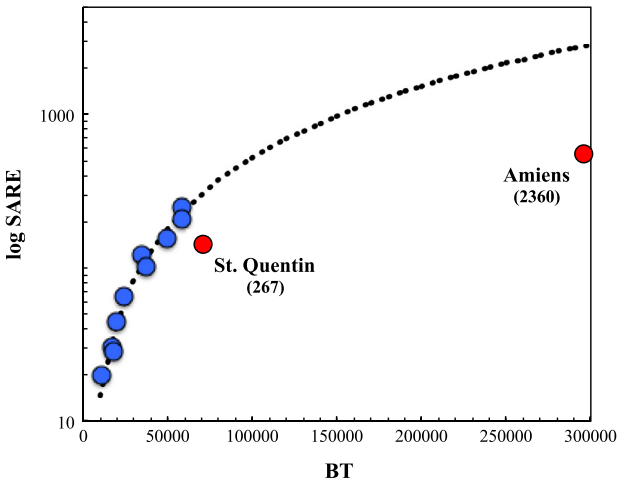

Fig. 1. Relationships between the total numbers of blood transfusions (BT) performed in 12 French hospitals of the Picardie State between 2004 and 2015 and the subsequent severe adverse reactions and events (SARE). Ten hospitals (blue dots) are highly significantly ($p < 0.01$) described by a power-law function $SARE \propto BT^{1.53}$ $(\cdots)$, while two (Saint Quentin and Amiens) drastically differ (red dots). The numbers given in parenthesis are the number of SARE predicted by the power-law function $SARE \propto BT^{1.53}$ for these two hospitals, showing that this equation strongly over-estimate their actual SARE. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

relatively slower than in hospitals performing less transfusions. In addition, the hospitals described by the power-law $SARE_{2004-2015} \propto (BT_{2004-2015})^{1.53}$ typically performed less than 60,000 blood transfusions over the 2004–2015 study period. In contrast, Saint Quentin and Amiens respectively performed 71,155 and 295,818 blood transfusions between 2004 and 2015. These observations may indicate the existence of a critical threshold beyond which the amount of performed blood transfusions induce relatively less unexpected or undesirable effects and/or the prevention of the occurrence of adverse effects is more efficient.

To refine this hypothesis, we subsequently investigated the potential relationship between yearly BT and the related SARE reported in the 12 studied hospitals from 2004 to 2015. We consistently found that SARE was significantly ($p < 0.01$) described by a power-law function of the form $SARE \propto BT^{1.44}$ from 2004 to 2015 for 10 of the 12 hospitals considered. The occurrence of SARE in the two other hospitals is strongly over-estimated by this power-law, though it is also significantly ($p < 0.01$) described by another power-law, $SARE \propto BT^{1.11}$ (Fig. 2). These results confirm that the relative occurrence of SARE is a function of the amount of blood transfusions performed. Specifically, our results show the existence of two distinct regimes in the occurrence of SARE depending of the quantity of blood transfusion performed, with a shift occurring for BT in the range 4200–5700 transfusions per year (Fig. 2). Note that this range has be determined empirically from the highest and lowest BT values fitting the power-laws $SARE \propto BT^{1.44}$ and $SARE \propto BT^{1.11}$.

Finally, we investigated the nature of the relationship between SARE and BT through separate yearly analyses, and found four distinct patterns depending on the year considered (Fig. 3, Table 2):

Table 2
List of the hospitals considered in the present work, where the yearly relationship between the amount of blood transfusions (BT) they performed and the subsequent severe and adverse reaction events (SARE) was a power-law function (*i.e.* SARE $\propto$ BT$^{\beta}$) or a linear function (*i.e.* SARE = aBT + b). The asterisks identify the N hospitals belonging to the observed power-laws and linear function.

Year	SARE $= \alpha \mathrm{BT}^{\beta}$			SARE $= a\mathrm{BT} + b$			Hospitals											
	α	β	N	a	b	N	Abbeville	Amiens	Beauvais	Château-Thierry	Chauny	Compiègne	Creil	Laon	Senlis	Soissons	St. Come	St. Quentin
2004	$6.6\ 10^{-4}$	0.9	10	–	–	–	*		*	*	*	*	*	*	*	*	*	
2005	–	–	–	$7.4\ 10^{-3}$	−5.52	10	*		*	*	*	*	*	*	*	*	*	
2006	–	–	–	$5.0\ 10^{-3}$	−2.59	10	*		*	*	*	*	*	*	*	*	*	
2007	–	–	–	$5.2\ 10^{-3}$	−3.5	10	*		*	*	*	*	*	*	*	*	*	
2008	$6.0\ 10^{-5}$	1.49	10	–	–	–	*		*	*	*	*	*	*	*	*	*	
2009	$2.0\ 10^{-6}$	1.92	10	–	–	–	*		*	*	*	*	*	*	*	*	*	
2010	$3.0\ 10^{-5}$	1.57	10	–	–	–	*		*	*	*	*	*	*	*	*	*	
2011	$5.0\ 10^{-6}$	1.76	10	–	–	–	*		*	*	*	*	*	*	*	*	*	
2012	$2.0\ 10^{-5}$	1.65	10	–	–	–	*		*	*	*	*	*	*	*	*	*	
2013	$2.0\ 10^{-5}$	1.60	10	–	–	–	*		*	*	*	*	*	*	*	*	*	
2014	$1.0\ 10^{-5}$	1.65	10	–	–	–	*		*	*	*	*	*	*	*	*	*	
2015	$5.0\ 10^{-4}$	1.17	12	–	–	–	*	*	*	*	*	*	*	*	*	*	*	*

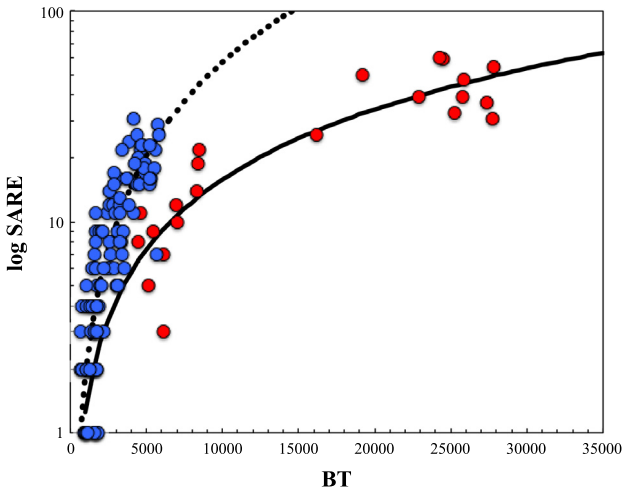

Fig. 2. Relationship between the yearly numbers of blood transfusions (BT) performed in 12 French hospitals of the Picardie State from 2004 to 2015 and the subsequent severe adverse reactions and events (SARE). Two distinct regimes occur above and below a critical threshold occurring around 5000 blood transfusions per year, with 10 hospitals (blue dots) described by a power-law function SARE $\propto$ BT$^{1.44}$ ($\cdots$) and two hospitals (red dots) described by a near-linear power-law SARE $\propto$ BT$^{1.11}$ (—). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(i) in 2004, SARE were significantly ($p < 0.05$) described by a power-law of the form SARE $\propto$ BT$^{0.9}$ in all hospitals but Amiens and Saint Quentin;
(ii) from 2005 to 2007, the relationship between SARE and BT was significantly ($p < 0.05$) described by a linear relation (*i.e.* SARE $= a$BT $+ b$) to BT in all hospitals but Amiens and Saint Quentin;
(iii) from 2008 to 2014, SARE were significantly ($p < 0.05$) described by a power-law of the form SARE $\propto$ BT$^{\beta}$ in all hospitals but Amiens and Saint Quentin β ranging between 1.49 and 1.92;
(iv) in 2015, the relationship between SARE and BT was significantly described by a power-law SARE $\propto$ BT$^{1.17}$ for the 12 hospitals considered.

Note that the upper limits of validity of both power-law and linear functions were consistently in the range 4200–5700 blood transfusions per year.

3. Discussion: size does matter in the evaluation of haemovigilance processes

Our results first suggest that the occurrence of SARE can be predicted by the amount of blood transfusions, irrespective of the amount of transfusions performed. More specifically, we show the existence of two distinct regimes in the occurrence of SARE depending of the quantity of blood transfusion performed. These two regimes may be directly linked to hospital-driven differences in the SARE reporting system, which have direct implications for the improvement of haemovigilance and transfusion safety. In particular, the optimization of the reporting work of haemovigilance correspondents (HR) allowed by time fully allocated to haemovigilance in large structures such as Amiens and Saint Quentin may contribute to improve the quality of the haemovigilance reporting system. In comparison, in smaller structures where HR are either pharmacists or medical practitioners no specific time is dedicated to haemovigilance. The critical threshold identified between the two scaling regimes (see Fig. 2) that occur in the range 4200–5700 transfusions per year may hence be related to a dysfunction in one or several of the steps involved in the identification and declaration of SARE. In this context, our results suggest that the occurrence and recurrence of SARE are significantly relatively more frequent in hospitals performing less blood transfusions. Note, however, that the slower evolution of SARE in the two hospitals performing the most transfusions may also happens because, in general, creating and operating the same infrastructure at higher densities is more efficient, more economically viable, and often leads to higher-quality services and solutions that are impossible in smaller places [3]. More specifically, these regimes may also be directly related to a difference in the quality of the blood products transfused, the skill level of blood transfusion practitioners and the related best practices followed in hospitals of different sizes. Further work is, however, needed to evaluate to what extent SARE and the observed power-laws follow from human error, and to what extent human learning can diminish the error rate. For instance, a variable worthy of further investigation in this context is the quality of the hospitals. This information, coupled with an area-specific economic indicator of wealth, could provide further insight into our conjecture that there is an increased efficiency with increasing BT, which would also suggest a doctor-learning/hospital-quality effect. The inter-annual fluctuations observed in the relationship between BT and SARE as well as the shifts between power-laws and linear functions (Fig. 3, Table 2) further indicate that the mechanisms driving

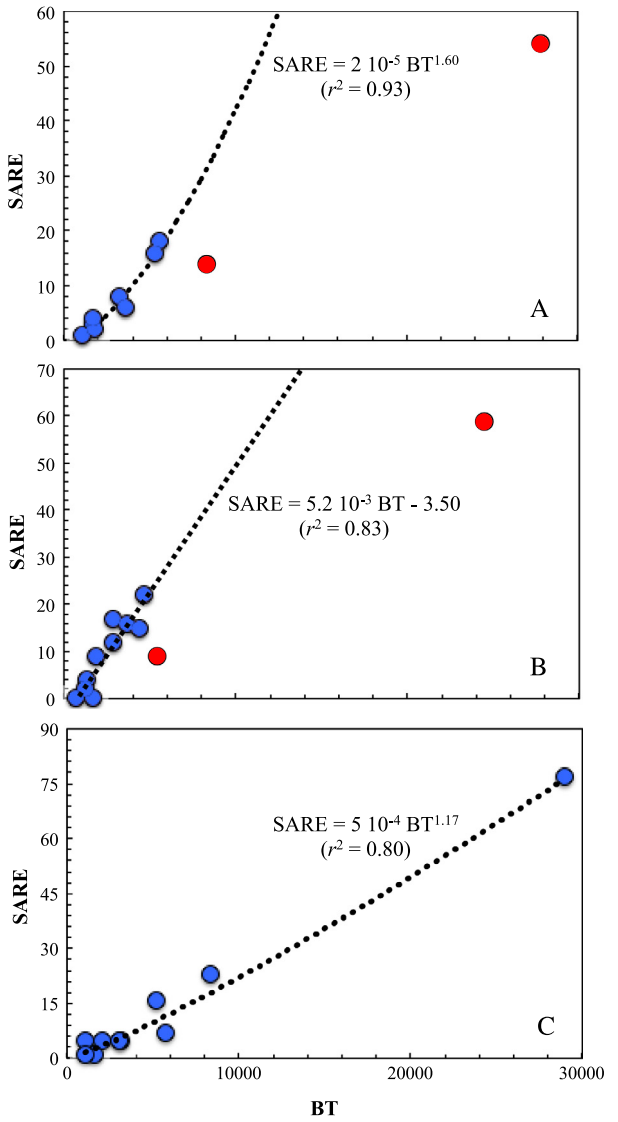

Fig. 3. Illustration of the different yearly patterns found in the relationship between the number of blood transfusions (BT) performed in 12 French hospitals of the Picardie State and the subsequent severe adverse reactions and events (SARE) from 2004 to 2015. Ten hospitals (blue dots) are described by a power-law function in 2004 and from 2008 to 2014 (2013 shown in A) or a linear function from 2005 to 2007 (2006 shown B), while two (Saint Quentin and Amiens; red dots) strongly diverge from it. Alternatively, all hospitals were significantly described by a power-law function with $\beta = 1.17$ in 2015 (C). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the observed dynamics of SARE are temporally drastically fluctuating. More fundamentally, these results imply that the haemovigilance process was somehow pathological from 2005 to 2007 where the relationship between SARE and BT was linear, as any departure from a power-law behavior has widely been considered as a sign of impairment and dysfunction in medical sciences [29], and in various areas of the natural sciences [21]. However, we could not find any changes in the variables driving the haemovigilance system before and after the 2005–2007 period. Specifically, no funding cut occurred and no different or new technology were introduced over the duration of our study. This suggests that this remarkable deviation from a power law may have more insidious origins that warrant the need for further work. Especially, generalizing our state-based approach at the national level would be a first step to assess if the dynamic observed in the present work are related to area-specific economic indicator of wealth or are more general, in which case they may be generalized at the national level, and eventually at larger scales. The exponents of the power-laws observed between SARE and BT are essentially greater than one (*i.e.* from 2008 to 2015; Table 2). This observation indicates that the number of unexpected or undesirable effects resulting from the therapeutic use of labile blood products increases relatively faster than the number of transfusions, which is a behavior consistent with observations conducted on various systems including a range of organisms, cities, economies and companies [47]. Specifically, the range of exponents observed in this study are bounded between

1.17 and 1.92; doubling the amount of blood transfusions then leads to increase the related severe adverse reactions and events by 125 to 278%. These figures are drastically different from the approximate 15% increase nearly universally reported (i) in a range of social-economic quantities such as wages, GDP, number of patents produced and number of educational and research institutions, and the related negative metrics such as negative metrics including crime, traffic congestion and incidence of certain diseases [48,49], and (ii) in biological systems such as small ant colonies which also been shown to live faster, die younger and burn up more energy than their larger counterparts, as do the individual ants that make up those colonies [50]. In turn, the power-law observed between SARE and BT was characterized by an exponent of 0.9 in 2004. This result fundamentally implies that doubling the number of blood transfusions only generates a 87% increase in SARE. Though still divergent from the 'universal 15% increase rule', this result indicates that in 2004 the studied process of haemovigilance was more efficient than from 2005 to 2015, and instead followed a 15% decrease rule.

It is finally noticeably stressed that the power-law function observed for Saint Quentin and Amiens, *i.e.* SARE $\propto$ BT$^{1.11}$ (Fig. 2), does not significantly differ (Analysis of Covariance, $p > 0.05$) from the power-law obtained for all hospitals in 2015, *i.e.* SARE $\propto$ BT$^{1.16}$ (Fig. 3c). This fact may indicate that the 12 hospitals considered in the present work converged towards a similar vigilance process, and that the whole transfusion chain from the collection of blood and its components to the follow up of its recipients followed the same dynamics in 2015 irrespective of the amount of blood transfusions performed.

4. Conclusions

The identification of a power-law signature in a vigilance process should be considered as a sign of robustness by analogy with the power-law behaviors exhibited by a range of biological and physical systems, where they are considered as adaptive because they serve as an organizing principle for highly complex, nonlinear processes, avoid restricting a functional response to highly periodic behavior, and are also an indication of error tolerance, as they allow to cope with stress and unpredictable environments [30]. As such, any departure from a power-law behavior between BT and SARE, and more generally in any vigilance process, should be considered as a sign of impairment and dysfunction [21,29], and should subsequently be considered as an early warning signal [30,51]. More generally, an attempt to generalize our state-based approach at the national level would be a first step to assess if the dynamics observed in the present work are related to area-specific economic indicator of wealth or are more general, in which case they may be generalized at the national level, and eventually at larger scales. It is finally stressed that the relevance of our hypothesis and exemplar results goes far beyond transfusion science and medical and pharmaceutical vigilances as they potentially have ramifications in any scenarios for medicine and research donations such as emergency aid, long-term aid, or assistance to national health systems or to individual health facilities *sensu* World Health Organization [52].

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