**Staphylococcus capitis** isolated from bloodstream infections: a nationwide 3-month survey in 38 neonatal intensive care units

Marie Decalonne¹, Sandra Dos Santos², Rémi Gimenes¹, Florent Goube¹, Géraldine Abadie³, Saïd Aberrane⁴, Vanina Ambrogī⁵, Raoul Baron⁶, Patrick Barthélemy⁷, Isabelle Bauvin⁸, Olivier Belmonte⁹, Emilie Benabid¹⁰, Rafik Ben Ammar¹¹, Salma Ben Hadj Yahia¹², Yasmina Berrouane¹³, Philippe Berthelot¹⁴, Alain Beuchée¹⁵, Emmanuelle Bille¹⁶, Pascal Bolot¹⁷, Stéphanie Bordes-Couecou¹⁸, Antoine Bouissou¹⁹, Sandra Bourdon²⁰, Nadège Bourgeois-Nicolaos²¹, Sophie Boyer²², Christian Cattoën²³, Vincent Cattoir²⁴, Chantal Chaplain²⁵, Céline Chatellet²⁶, Aurore Claudinon²⁷, Nathalie Chautemps²⁸, Hélène Cormier²⁹, Céline Coroller-Bec³⁰, Benjamin Cotte³¹, Carole De Chillaz³², Olivier Dauwalder³³, Aude Davy³⁴, Martine Delorme³⁵, Maryvonne Demasure³⁶, Luc Desfrere³⁷, Michel Drancourt³⁸, Clarisse Dupin³⁹, Véronique Faraut-Derouin⁴⁰, Arnaud Florentin⁴¹, Virginie Forget⁴², Nicolas Fortineau⁴³, Tania Foucan⁴⁴, Pierre Frange⁴⁵, Karine Gambarotto⁴⁶, Géraldine Gascoin⁴⁷, Laure Gilbert⁴⁸, Jacques Gilquin⁴⁹, Audrey Glanard⁵⁰, Jacqueline Grando⁵¹, Alain Gravet⁵², Jérôme Guinard⁵³, Geneviève Hery-Arnaud⁵⁴, Nadia Idri⁵⁵, Jean-Marc Jellimann⁵⁶, Olivier Join-Lambert⁵⁷, Sylvie Joron⁵⁸, Philippe Jouvencel⁵⁹, Marie Kempf⁶⁰, Sophie Ketterer-Martinson⁶¹, Mouna Khecharem⁶², Serge Klosowski⁶³, Franck Labbe⁶⁴, Adeline Lacazette⁶⁵, Fabrice Lapeyre⁶⁶, Jérôme Larche⁶⁷, Peggy Larradou⁶⁸, Anne Le Pourhienne⁶⁹, Novenn Le Sache⁷⁰, Sylvie Ledru⁷¹, Annick Lefebvre⁷², Clément Legeay⁷³, Florence Lemann⁷⁴, Claire Lesteven⁷⁵, Marion Levast-Raffin⁷⁶, David Leysse⁷⁷, Isabelle Ligi⁷⁸, Alain Lozniewski⁷⁹, Pierre Lureau⁸⁰, Franck-Olivier Mallaval⁸¹, Edith Malpote⁸², Stéphane Marret⁸³, Pascale Martres⁸⁴, Guillaume Menard⁸⁵, Laura Merviel⁸⁶, Laurent Mereghetti⁸⁷, Véronique Merle⁸⁸, Pascale Minery⁸⁹, Virginie Morange⁹⁰, Julien Mourdie⁹¹, Anaëlle Muggeo⁹², Jean Nakhleh⁹³, Marie-Noëlle Noulard⁹⁴, Claude Olive⁹⁵, Hugues Patural⁹⁶, Pascale Penn⁹⁷, Manuel Petitfrere⁹⁸, Bruno Pozetto⁹⁹, Audrey Robine¹⁰⁰, Christine Roques Ceschin¹⁰¹, Raymond Ruyimy¹⁰², Amine Siali¹⁰³, Stéphanie Soive¹⁰⁴, Souad Slimani¹⁰⁵, Anne-Sophie Trentesaux¹⁰⁶, Dominique Trivier¹⁰⁷, Christian Vandenbussche¹⁰⁸, Laurent Villeneuve¹⁰⁹, Evelyne Werner¹¹⁰, Stéphane Le Vu¹¹¹, Nathalie Van Der Mee-Marquet¹,²

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**Abstract**

To increase the knowledge about *S. capitis* in the neonatal setting, we conducted a nationwide 3-month survey in 38 neonatal intensive care units (NICUs) covering 56.6% of French NICU beds. We demonstrated 14.2% of *S. capitis* BSI (*S.cap*BSI) among nosocomial BSIs. *S.cap*BSI incidence rate was 0.59 per 1000 patient-days. A total of 55.0% of the *S. capitis* strains isolated from bloodstream infections: Staphylococcus capitis (NICU) among neonates [1]. The prevention of the avoidable

**Keywords** *Staphylococcus capitis* · NRCS-A clone · Bloodstream catheter-related infection · Neonatal Intensive Care Unit (NICU) · Preterm babies · Neonates · Nationwide active surveillance

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**Introduction**

Catheter-related bloodstream infections (CRBSI) are associated with increased rates of morbidity in intensive care unit patients and in neonates [1]. The prevention of the avoidable
part of CRBSIs is a public health priority [2, 3]. In this context, since 2019, all French hospitals and clinics are encouraged to participate in an annual 3-month survey of CRBSI coordinated by the national infection control SPIADI network. Over the last two decades, multidrug-resistant *Staphylococcus capitis* has been increasingly reported as a major agent responsible for CRBSI in preterm babies [4]. Therapeutic failures likely due to heteroresistance to vancomycin in this bacterium [5] and local epidemics have been identified and investigated in NICUs [5–7]. *S. capitis* seems to be particularly well-adapted to the NICU environment, possibly in connection with its ability to produce biofilm [8, 9]. However, the neonate contamination routes remain obscure. Recent studies performed in distinct parts of the world have demonstrated a single lineage within the *S. capitis* species, named NRCS-A, responsible for invasive neonatal infections worldwide [10, 11]. The mechanisms that have driven the global dissemination of this clone have not yet been elucidated. We report the results of the 3-month nationwide BSI survey conducted during the first quarter of 2019 in the largest series of NICUs located in 38 French hospitals. We present clinical data related to the neonates suffering from BSI, and the incidence rates and major characteristics of the neonatal BSIs. In addition, using molecular methods, we characterized the isolates responsible for *S. capitis* BSIs to establish whether or not they belong to the NRCS-A clone. We provide new data that increase the knowledge about *S. capitis* in the current neonatal setting.

**Materials and methods**

**BSI epidemiological survey method**

**Study population** Thirty-eight maternity hospitals comprising neonatal intensive beds participated in the study (Fig. 1). The 447 beds surveyed represented 56.6% of French neonatal intensive beds (https://www.data.gouv.fr/en/datasets/).

**Study design** The surveillance program involved a 3-month survey of all cases of nosocomial BSI between January 1 and April 30 2019. The survey covered 33,971 intensive care patient-days (PD). Nosocomial BSIs were defined according to international definitions (CDC). The variables studied included clinical data (i.e., sex, gestational age, birth weight, death within 7 days of BSI diagnosis), major characteristics of the BSI such as the portal of entry (skin [primitive cutaneous form or superinfection of a skin breach], lungs, urine, intravascular device, or digestive tract), and for catheter-related BSI, the time lag between the insertion of the catheter, and the appearance of the clinical signs of the BSI. The BSI incidence rates were calculated per 1000 PD. Ethical approval of the surveillance program was obtained at the national level from the Réseau de Prévention des Infections Associées aux Soins.

**Microbiological study** PFGE was used as a typing technique [12].

**Statistical data** The data were analyzed with R software. Chi-square tests and Fisher’s exact test (two-tailed) were used to test associations, and a *P* value of 0.05 was considered significant.

**Results**

**Epidemiology of neonatal BSI** During the study period, 141 nosocomial BSIs were diagnosed in 81 male and 60 female neonates. The mean BSI incidence rate was 4.15 per 1000 PD (Table 1). The most frequently isolated micro-organisms were *S. epidermidis* (39.0%), *S. aureus* (17.0%), *S. haemolyticus* (15.6%), and *S. capitis* (14.2%). Twenty BSIs were polymicrobial (14.2%).

The portal of entry of the BSIs was suspected or proven in 83.7% of the cases. The digestive tract (12.1%), the skin (8.5%), and the pulmonary tract (6.4%) were minor portals of entry. Most of the BSIs were catheter-related (70 CRBSIs; 50.0 %) (Table 2). The CRBSI involved a central venous catheter (CVC) in 47 cases (67.1%), all but one associated with *staphylococci* (97.9%), and an umbilical venous catheter (UVC) in 23 cases (32.9%). The UVC-related BSIs were more diverse than those related to CVC: *enterococci-, Enterobacteriaceae-, and B. cereus*-BSIs
Table 1  BSI, B-cvc, and B-uvc incidence rates per 1000 PD according to the participating centers

| Participating centers with a neonatal intensive care unit | BSI incidence rates per 1000 PD | B-cvc | B-uvc |
|---------------------------------------------------------|---------------------------------|-------|-------|
| University regional hospitals                           | All S. aureus S. epidermidis S. capitis Enterobacteriaceae | All S. aureus B-cvc S. capitis B-cvc | All |
| 1 2,443 10                                              | 4.09 0.82 2.45 0.41 0.00       | 1.64 0.41 | 0.41 2.46 |
| 2 1,840 7                                               | 3.80 1.09 0.54 0.00 1.63       | 1.63 0.54 | 0.00 0.54 |
| 3 1,825 10                                              | 5.48 2.19 1.64 0.00 0.55       | 0.00 0.00 | 0.00 0.00 |
| 4 1,658 14                                              | 8.44 2.41 4.22 0.60 0.60       | 3.01 1.21 | 0.60 0.60 |
| 5 1,482 6                                               | 4.05 0.67 0.00 2.02 0.00       | 1.35 0.67 | 0.67 0.00 |
| 6 1,332 8                                               | 6.01 0.00 3.00 1.50 1.50       | 3.00 0.00 | 0.75 1.50 |
| 7 1,322 10                                              | 7.56 0.76 3.02 0.76 0.76       | 0.00 0.00 | 0.00 0.00 |
| 8 1,294 0                                               | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 9 1,134 8                                               | 7.05 0.00 2.64 1.76 0.00       | 3.53 0.00 | 0.88 0.88 |
| 10 1,114 0                                              | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 11 1,062 0                                              | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 12 1,023 6                                              | 5.86 0.00 2.93 0.98 0.00       | 0.98 0.00 | 0.98 1.95 |
| 13 1,016 3                                              | 2.97 0.98 0.98 0.98 0.00       | 0.98 0.00 | 0.98 0.98 |
| 14 999 3                                                | 3.00 0.00 2.00 0.00 0.00       | 1.00 0.00 | 0.00 0.00 |
| 15 892 4                                                | 4.48 0.00 1.12 2.24 1.12       | 2.24 0.00 | 1.12 1.12 |
| 16 822 0                                                | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 17 764 5                                                | 6.54 1.31 3.93 1.31 0.00       | 2.62 0.00 | 0.00 0.00 |
| 18 793 5                                                | 6.31 1.26 2.52 1.26 0.00       | 3.78 0.00 | 1.26 0.00 |
| 19 636 0                                                | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 20 545 4                                                | 11.00 0.00 0.00 1.83 0.00      | 5.50 0.00 | 0.00 1.83 |
| 21 524 0                                                | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| General hospitals                                        | 3.09 1.03 1.03 1.03 0.00       | 2.06 1.03 | 1.03 1.03 |
| 22 972 3                                                | 1.12 0.00 0.00 1.12 0.00       | 1.12 0.00 | 1.12 0.00 |
| 23 893 1                                                | 5.62 2.25 2.25 1.12 1.12       | 1.12 1.12 | 0.00 1.12 |
| 24 890 5                                                | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 25 769 0                                                | 7.97 3.98 0.00 1.33 2.66       | 1.33 1.33 | 0.00 0.00 |
| 26 753 6                                                | 3.36 0.00 1.68 0.00 0.00       | 1.68 0.00 | 0.00 0.00 |
| 27 595 2                                                | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 28 570 0                                                | 12.20 0.00 6.08 0.00 0.00      | 2.03 0.00 | 0.00 10.14 |
| 29 493 6                                                | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 30 401 0                                                | 2.52 0.00 2.52 0.00 0.00       | 2.52 0.00 | 0.00 0.00 |
| 31 396 1                                                | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 32 369 0                                                | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 33 353 2                                                | 2.68 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 34 320 3                                                | 9.38 0.00 6.25 3.12 0.00       | 0.00 0.00 | 0.00 0.00 |
| 35 308 7                                                | 22.72 0.00 9.74 6.49 0.00      | 9.74 0.00 | 0.00 0.00 |
| 36 275 2                                                | 7.27 3.64 3.64 3.64 0.00       | 3.64 3.64 | 0.00 0.00 |
| Participating centers with intensive care beds in neonatal medical unit | | | |
| General hospital                                        | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| 22 854 0                                                | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
| Private clinic                                           | 0.00 0.00 0.00 0.00 0.00       | 0.00 0.00 | 0.00 0.00 |
Table 1 (continued)

| PD | Nosocomial BSI | BSI incidence rates per 1000 PD | B-cvc | B-uvc |
|----|----------------|---------------------------------|-------|-------|
| PD | BSI            | All                             | S. aureus | S. epidermidis | S. capitis | Enterobacteriaceae | All | S. aureus B-cvc | S. capitis B-cvc | All |
| 40 | 330            | 0.00                            | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.38 | 0.29 | 0.68 |
| All| 33,971         | 141                             | 4.15 | 0.71 | 1.62 | 0.59 | 0.50 | 1.38 | 0.26 | 0.29 |

Table 2  Major characteristics of the BSIs and infected neonates according to the micro-organism

| BSIs     | N  | Portal of entry | Sex | Birth weight (g) | Gestational age (week) | Early death (%) |
|----------|----|-----------------|-----|------------------|------------------------|-----------------|
|          |    | CVC | UVC | Cutaneous | Pulmonary | Urinary | Digestive | Others | Not identified | Male | Female | < 1500 g | Median | < 33 weeks | Median |
| All      | 141 | 47  | 23  | 12         | 9         | 1       | 17       | 9       | 23            | 81   | 60     | 112 (79.4) | 980    | 113 (80.1) | 28    |
| S. aureus| 24  | 9   | 4   | 4          | 4         | 1       | 1        | 1       | 12            | 12   | 12     | 16 (66.7)  | 1,100  | 16 (66.7)  | 30    |
| S. epidermidis| 55 | 20  | 11  | 6          | 1         | 4       | 1        | 12       | 35            | 20   | 20     | 43 (78.2)  | 910    | 43 (78.2)  | 27    |
| S. haemolyticus| 22 | 10  | 3   | 6          | 2         | 3       | 1        | 3        | 10            | 12   | 10     | 22 (100.0) | 917    | 21 (95.4)  | 27    |
| S. capitis | 20  | 10  | 1   | 1          | 1         | 3       | 4        | 12       | 8             | 8    | 8      | 16 (80.0)  | 855    | 15 (75.0)  | 26    |
| Enterococci| 7  | 1   | 3   | 1          | 1         | 1       | 1        | 6        | 1             | 4    | 1      | 4 (57.1)   | 1,260  | 4 (57.1)   | 31    |
| Enterobacteriaceae| 17 | 1   | 2   | 2          | 1         | 4       | 5        | 2        | 9             | 8    | 9      | 9 (52.9)   | 1,480  | 11 (64.7)  | 29    |
| Bacillus cereus | 3  | 1   | 1   | 1          | 1         | 1       | 1        | 1        | 0             | 3    | 0      | 2 (66.7)   | 745    | 3 (100.0)  | 28    |
were more frequent with UVC-BSIs (26.1%) rather than with CVC-BSIs (4.3%) \((p = 0.022)\). The median time lag between the insertion of the catheter and the appearance of the clinical signs of the BSI was significantly longer for \(S. \text{capitis} (63.6\%, \geq 10 \text{ days})\) rather than for \(S. \text{aureus} (7.7\%), S. \text{epidermidis} (16.1\%), S. \text{haemolyticus} (30.8\%), \text{enterococci}, \text{and Enterobacteriaceae} \text{no case} \)(\(p = 0.018\); Table 3).

**Characteristics of the infected neonates** The gestational age of the infected neonates ranged between 24 and 41 weeks (median value 28), and their birth weight ranged between 455 and 4050 g (median value 1100); 15.6% of the neonates died during the 7-day period after the diagnosis of the BSI. BSIs involving \(S. \text{aureus}, \text{Enterobacteriaceae}, \text{and Enterococci} \) were associated with the highest prevalence of early death among infected neonates (29.4, 29.2, and 14.3% for \text{Enterobacteriaceae}-, \(S. \text{aureus}-, \text{and Enterococci-associated BSIs, respectively). The prevalence of BSI in the neonates with the a gestational age \geq 33 \text{ weeks and a birth weight} > 1500 \text{ g differed according to the bacteria (Table 2); it was the highest for Enterococci (42.9\%), Enterobacteriaceae (35.3\%), and S. \text{aureus} (29.2\%), lower for S. \text{capitis} (20.0\%) and E. \text{epidemidis} \text{18.2\% and nil for S. \text{haemolyticus and B. cereus} (p = 0.056). S. \text{capitis BSI characteristics and antibiotic susceptibility of S. \text{capitis strains}} Twenty BSIs were associated with \(S. \text{capitis} (14.2\%), \text{resulting in a mean incidence of} 0.59 \text{ per 1000 PD, ranging between 0 and 2.24 according to centers.**

| Micro-organism | Number of CRBSIs | Time lag (days) | Mean | Median | < 10 days | \(\geq 10 \text{ days} \)
|----------------|------------------|----------------|------|--------|----------|---------|
| \(S. \text{aureus}\) | 13 | 7.2 | 6 | 11 | 3 |
| \(S. \text{epidermidis}\) | 31 | 8.0 | 6 | 26 | 5 |
| \(S. \text{haemolyticus}\) | 13 | 8.1 | 6 | 9 | 4 |
| \(S. \text{capitis}\) | 10 | 10.3 | 10 | 4 | 7 |
| Enterococci | 4 | 6.2 | 6 | 4 | 0 |
| Enterobacteriaceae | 3 | 4 | 4 | 3 | 0 |

**Table 4** Antibiotic susceptibility of the \(S. \text{capitis}\) strains

| Centers | Strain | Antibiotype\(^a\) | MIC vancomycine (mg/L) | MIC teicoplanine (mg/L) |
|---------|--------|-------------------|------------------------|------------------------|
| 1 | 1 | Oxa KTG Ri Fu | 0.5 | < 0.25 |
| 9 | 2 | Oxa KTG Ri Fo | 0.5 | < 0.25 |
| 3 | Oxa KTG Ri Fo | 0.5 | < 0.25 |
| 4 | 4 | Oxa KTG Ri Fo | – | – |
| 7 | 5 | Oxa AKTG Ri Fu Ery | – | – |
| 13 | 6 | Oxa TG Nor | 1 | 2 |
| 6 | 7 | Oxa G Cip Ery Ri | < 4 | < 2 |
| 8 | Oxa G Cip Ery | < 4 | < 2 |
| 5 | 9 | Oxa ATG Ri Fo Te(I) Ery(I) Pr(I) | 1 | 0.5 |
| 10 | Oxa ATG Ri Fo Te(I) Ery(I) Pr(I) | 1 | 0.5 |
| 11 | Oxa ATG Ri Fo Te(I) Ery(I) Pr(I) | 1 | 0.5 |
| 15 | 12 | Oxa ATG Cip Fo | 1 | 2 |
| 13 | Oxa ATG Cip Fo | 1 | 1 |
| 17 | 14 | Oxa AKTG Cip Fo | 1 | 1 |
| 12 | 15 | Oxa KTG Ery | 2 | 4 |
| 22 | 16 | Oxa AKTG | 0.5 | < 0.25 |
| 18 | 17 | Oxa ATG Ri Fu | 0.5 | < 0.25 |
| 26 | 20 | Oxa ATG Ri Fo Te(I) Ery(I) Pr(I) | 1 | 2 |

\(\text{Oxa oxacillin, K kanamycin, T tobramycin, G gentamicin, A amikacin, Ri Rifampicin, Fu fusidic acid, Fo fosfomycin, Te tetracyclin, Ery erythromycin, Pr pristinamycin, Nor norfloxacin, Cip ciprofloxacin}\)
Table 1; 39.5% of the NICUs reported at least one *S. capitis*-BSIs. The *S. capitis*-BSIs were significantly associated with the largest NICUs: at least one *S. capitis*-BSIs was reported in 15 of the 22 NICUs with ≥ 10 beds, whereas none was reported in the 14 NICUs with < 10 beds (p < 0.001). Four NICUs documented two (n = 3) or three (n = 1) *S. capitis*-BSIs during the survey period. The antibiotic susceptibility patterns of 18 strains were available (90.0%). Most of the strains were resistant to multiple antibiotics, i.e., methicillin (100%), gentamicin (100%), rifampicin (61.1%), fosfomycin (55.5%), erythromycin (44.4%), fluoroquinolones (33.3%), and fusidic acid (22.2%). Vancomycin and teicoplanin MIC values ranged between 0.25 and 4 mg/L (Table 4). Data regarding antibiotic treatment were available for 18 cases: 17 neonates received vancomycin over 2–24 days (median value: 8 days) and the remaining neonate received linezolid (11 days). A favorable outcome was observed in all but one case. An early death was observed for a preterm infected neonate (gestational age 25 weeks; birth weight 455 g), who received vancomycin over 3 days following the detection of a *S. capitis* and *S. haemolyticus*-associated CRBSI.

Twelve *S. capitis* BSI strains from 8 NICUs were available for molecular typing. A considerable homogeneity was demonstrated among the strains, and PFGE pattern analysis demonstrated that all strains belonged to the NRCS-A clone [10] (Fig. 2). Regarding the three NICUs that reported several *S. capitis*-BSI cases, the strains isolated in a same center shared the same pattern in two cases. In addition, the strains isolated from three distinct centers located in two distant French regions shared the same pattern.

**Discussion**

This nationwide study adds several elements to the available data on *S. capitis* responsible for neonatal BSI.

We provide a first mean incidence of *S. capitis* BSIs in French NICUs. *S. capitis* BSIs currently involve an average of one neonate per 1700 PD, which is lower than that observed for *S. aureus* and *S. epidermidis*, but higher than that of Enterobacteriaceae in the population of neonates surveyed. Our findings confirm *S. capitis* as a significant agent responsible for nosocomial BSI in the neonatal setting [10, 11, 13].

Second, such as *S. epidermidis* and *S. haemolyticus*, we showed that *S. capitis* preferentially infects the more fragile neonates and thus confirmed that *S. capitis* is an opportunistic pathogen, devoid of great virulence potential. Concordant with previous studies [13], all the *S. capitis* strains responsible for BSIs displayed resistance to methicillin and gentamicin, but remained susceptible to vancomycin. *S. capitis*-BSIs have been taken into account by the clinicians, and vancomycin probably played a crucial role in the recovery of neonates.

Third, we identified one particularity distinguishing *S. capitis* among the bacteria associated with CRBSI cases. Our study reveals a doubled lag time between insertion of the catheter and the first signs of the BSI involving *S. capitis* when compared with other bacteria. The absence of early infection likely excludes
a contamination of the catheter at the time of its insertion, but rather indicates that the contamination of the catheter may have occurred following catheter manipulations among neonates presenting the longest periods of catheterization.

Finally, the molecular analysis of a large part of the *S. capitis* strains indicates that they belong to the multidrug-resistant NRCS-A clone and highly suggests likely epidemic phenomena among the NICUs presenting the highest incidence rates of *S. capitis* BSIs.

**Conclusion**

Our data confirm the clone NRCS-A particularly well-suited to the neonatal setting and its cumbersome epidemiology [10, 11, 13]. In most NICUs, *S. capitis* BSIs remain relatively infrequent among neonates, but concern primarily the most fragile ones. In order to better determine the factors involved in the occurrence of these infections, monitoring of BSIs should be continued and complemented by a systematic investigation when several cases are identified over a 3-month period in the same NICU.

**Authors’ contribution** MD conducted the study, SDS performed the molecular typing, RM conducted the statistical analysis, FG designed and developed the website for data collection and analysis, SLV participated with the data analysis, NVDM designed and conducted the study and wrote the manuscript.

All the others are participating members from each of the 41 NICUs (the infection control practitioner, the microbiologist, and the clinician responsible for the NICU). They collected the data and strains.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The nationwide survey was conducted under the control of the national agency Santé Public France and with the authorization by the CNIL (a national committee for data protection). Ethical review and approval was not required for the study on human participants in accordance with the French national legislation and institutional requirements.

**Informed consent** In each participating hospital, a quality commitment charter was signed by the general director and the infection control physician. Patients were informed and ask for consent about the 3-month national survey.

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Affiliations

Marie Decalonne 1, Sandra Dos Santos 2, Rémi Gimenes 1, Florent Goube 1, Géraldine Abadie 3, Saïd Aberrane 4, Vanina Ambrogi 5, Raoul Baron 6, Patrick Barthelemy 7, Isabelle Bauvin 8, Olivier Belmonte 9, Emilie Benabid 10, Rafik Ben Ammar 11, Salma Ben Hadj Yahia 12, Yasmina Berrouane 13, Philippe Berthelot 14, Alain Beuchee 15, Emmanuelle Bille 16, Pascal Bolot 17, Stéphanie Bordes-Couecou 18, Antoine Bouissou 19, Sandra Bourdon 20, Nadège Bourgeois-Nicolaos 21, Sophie Boyer 22, Christian Cattoen 23, Vincent Cattoir 24, Chantal Chaplain 25, Céline Chatelet 26, Aurore Claudinon 27, Nathalie Chautemps 28, Hélène Cormier 29, Céline Coroller-Bec 30, Benjamin Cotte 31, Carole De Chillaz 32, Olivier Dauwalder 33, Aude Davy 34, Martine Delorme 35, Maryvonne Demasure 36, Luc Desfriere 37, Michel Drancourt 38, Clarisse Dupin 39, Véronique Faraut-Derouin 40, Arnaud Florentin 41, Virginie Forget 42, Nicolas Fortineau 43, Tania Foucan 44, Pierre France 16,45, Karine Gambarton 46, Géraldine Gascon 47, Laure Gilbert 20, Jacques Gilquin 48, Audrey Glanard 49, Jacqueline Grando 50, Alain Gravet 51, Jérôme Guinard 52, Geneviève Hery-Arnaud 53, Claire Hurt 54, Nadia Idri 55,56, Jean-Marc Jellimann 57, Olivier Join-Lambert 58, Sylvie Joron 59, Philippe Jouvencel 60, Marie Kempf 61, Sophie Ketterer-Martinon 62, Mouna Khecharem 63, Serge Klosowski 64, Franck Labbe 65, Adeline Lacazette 66, Fabrice Lapeyre 67, Jérôme Larche 68, Peggy Larroude 69, Anne Le Pourhiennecc 70, Nolwenn Le Sache 71, Sylvie Ledru 72, Annick Lefebvre 73, Clément Legeay 79, Florence Lemann 74, Claire Lesteven 75, Marion Levast-Raffin 76, David Leyssene 77, Isabelle Ligi 78, Alain Lozniewski 79, Pierre Lureau 80, Franck-Olivier Mallaval 42, Edith Malpote 81, Stéphane Marret 82, Pascale Martres 83, Gaëlle Menard 84, Laura Menvielle 85, Laurent Mereghetti 86, Véronique Merle 87, Pascale Minery 88, Virginie Morange 89, Julien Mourdie 90, Amaelie Mougeot 91, Jean Nakhleh 92, Marie-Noëlle Noard 93, Claude Olive 94, Hugues Patural 95, Pascale Penn 96, Manuel Petitfrère 97, Bruno Pozetto 98, Brigitte Riviere 99, Audrey Robine 100, Christine Roques Ceschin 5, Raymond Ruimy 101, Amine Siali 102, Stéphanie Soive 103, Souad Slimani 104, Anne-Sophie Trentesaux 105, Dominique Trivier 26, Christian Vandenbussche 106, Laurent Villeneuve 107, Evelyne Werner 108, Stéphane Le Vu 109, Nathalie Van DerMee-Marquet 1,2

1 SPIADI, CPIAS CVDL, Hôpital Bretonneau, Centre Hospitalier Universitaire, 37044 Tours, France
2 Cellule d’Epidémiologie Régionale des Infections Nosocomiales, CPIAS CVDL, Service de Bactériologie-Virologie-Hygiène, Hôpital Trousseau, CHRU, 37044 Tours, France
3 Service de réanimation néonatale, Centre Hospitalier Universitaire Félix Guyon, 97400 Saint Denis de la Réunion, France
4 Laboratoire de Microbiologie, Centre Hospitalier Inter-Communal, 94010 Créteil, France
5 Équipe opérationnelle d’hygiène, Centre Hospitalier Universitaire, 31059 Toulouse, France
6 Équipe opérationnelle d’hygiène, Centre Hospitalier Universitaire, 29609 Brest, France
7 Équipe opérationnelle d’hygiène, Hôpital de la Conception, APHM, 13005 Marseille, France
8 Service de réanimation néonatale, Centre Hospitalier, 64000 Pau, France
9 Laboratoire de Microbiologie, Centre Hospitalier Universitaire Félix Guyon, 97400 Saint Denis de la Réunion, France
10 Équipe opérationnelle d’hygiène, Centre Hospitalier, 95300 Fontoise, France
11 Service de réanimation néonatale, Centre Hospitalier Universitaire Antoine-Béclère, APHP, 92140 Clamart, France
12 Laboratoire de Microbiologie, Centre Hospitalier, 62100 Calais, France
13 Équipe opérationnelle d’hygiène, Centre Hospitalier Universitaire, 06200 Nice, France
14 Équipe opérationnelle d’hygiène, Centre Hospitalier Universitaire, 42055 Saint Etienne, France
15 Service de réanimation néonatale, Centre Hospitalier Universitaire, 35000 Rennes, France
16 Laboratoire de Microbiologie clinique, Hôpital universitaire Necker-Enfants malades, APHP, 75015 Paris, France
17 Service de réanimation néonatale, Centre Hospitalier Delafontaine, 93205 Saint Denis, France
18 Équipe opérationnelle d’hygiène, Centre Hospitalier, 64100 Bayonne, France
19 Service de réanimation néonatale, Centre Hospitalier Universitaire, 37044 Tours, France
20 Équipe opérationnelle d’hygiène, Centre Hospitalier du Havre, 76290 Montivilliers, France
21 Laboratoire de Microbiologie, Centre Hospitalier Universitaire Antoine-Béclère, APHP, 92140 Clamart, France
22 Laboratoire de Microbiologie, Centre Hospitalier Universitaire Charles Nicolle, 76000 Rouen, France
68 Polyclinique Saint Roch, 34000 Montpellier, France
69 Équipe opérationnelle d’hygiène, Centre Hospitalier, 64000 Pau, France
70 Service de réanimation néonatale, Centre Hospitalier, 62100 Calais, France
71 Service de réanimation néonatale, Centre Hospitalier Universitaire, Kremlin Bicêtre, APHP, 94275 Le Kremlin Bicêtre, France
72 Laboratoire de Microbiologie, Centre Hospitalier, 62300 Lens, France
73 Équipe opérationnelle d’hygiène, Université de Reims Champagne-Ardenne, 51100 Reims, France
74 Équipe opérationnelle d’hygiène, Centre Hospitalier, 95107 Argenteuil, France
75 Équipe opérationnelle d’hygiène, Centre Hospitalier Universitaire, 14000 Caen, France
76 Laboratoire de Biologie Médicale, Centre Hospitalier Métropole Savoie-Site de Chambéry, 73 011 Chambéry, France
77 Laboratoire de Microbiologie, Centre Hospitalier, 64100 Bayonne, France
78 Service de réanimation néonatale, Centre Hospitalier Universitaire, Hôpital de la Conception, APHP, 13005 Marseille, France
79 Laboratoire de Microbiologie, Hôpitaux de Brabois, 54035 Nancy, France
80 Laboratoire de Microbiologie, Centre Hospitalier, 79021 Niort, France
81 Laboratoire de Microbiologie, Centre Hospitalier Universitaire, 97159 Pointe-à-Pitre, France
82 Service de réanimation néonatale, Centre Hospitalier Universitaire Charles Nicolle, 76000 Rouen, France
83 Laboratoire de Microbiologie, Centre Hospitalier, 95300 Pontoise, France
84 Équipe opérationnelle d’hygiène, Centre Hospitalier Universitaire, 35000 Rennes, France
85 Service de réanimation néonatale et réanimation pédiatrique, Centre Hospitalier Universitaire, Hôpital Robert Debré, Inserm UMR-S 1250 P3Cell, Université de Reims Champagne-Ardenne, 51100 Reims, France
86 Laboratoire de Microbiologie, Centre Hospitalier Universitaire, 37044 Tours, France
87 Équipe opérationnelle d’hygiène, Centre Hospitalier Universitaire Charles Nicolle, 76000 Rouen, France
88 Équipe opérationnelle d’hygiène, Centre Hospitalier, 68100 Mulhouse, France
89 Équipe opérationnelle d’hygiène, Centre Hospitalier Universitaire, 37044 Tours, France
90 Service de réanimation néonatale, Centre Hospitalier du Havre, 76290 Montivilliers, France
91 Laboratoire de Bactériologie, Université de Reims Champagne-Ardenne, 51100 Reims, France
92 Service de réanimation néonatale, Centre Hospitalier, 68100 Mulhouse, France
93 Laboratoire de Microbiologie, Centre Hospitalier, 62000 Arras, France
94 Laboratoire de Microbiologie, Centre Hospitalier Universitaire de Martinique, 97261 Fort de France, France
95 Service de réanimation néonatale, Centre Hospitalier Universitaire, 42055 Saint Etienne, France
96 Laboratoire de Microbiologie, Centre Hospitalier, 72000 Le Mans, France
97 Polyclinique Majorelle, 54000 Nancy, France
98 Laboratoire de Microbiologie, Centre Hospitalier Universitaire, 42055 Saint Etienne, France
99 Laboratoire de Microbiologie, Centre Hospitalier, 81100 Castres, France
100 Service de réanimation néonatale, Centre Hospitalier, 72000 Le Mans, France
101 Laboratoire de Microbiologie, Centre Hospitalier Universitaire, 06200 Nice, France
102 Équipe opérationnelle d’hygiène, Centre Hospitalier Inter-Communal, 94010 Créteil, France
103 Service de réanimation néonatale, Centre Hospitalier, 22000 Saint Brieuc, France
104 Équipe opérationnelle d’hygiène, Centre Hospitalier Universitaire de Martinique, 97261 Fort de France, France
105 Service de réanimation néonatale, Centre Hospitalier Universitaire, 14000 Caen, France
106 Équipe opérationnelle d’hygiène, Centre Hospitalier, 62000 Arras, France
107 Laboratoire de Microbiologie, Centre Hospitalier, 64000 Pau, France
108 Service de réanimation néonatale, Centre Hospitalier Régional, 45100 Orléans, France
109 Agence Santé Publique France, 94415 Saint Maurice, France