



# *mecC*-MRSA, Hedgehogs and dermatophytes

Anders Rhod Larsen

National Reference Laboratory for Antimicrobial Resistance

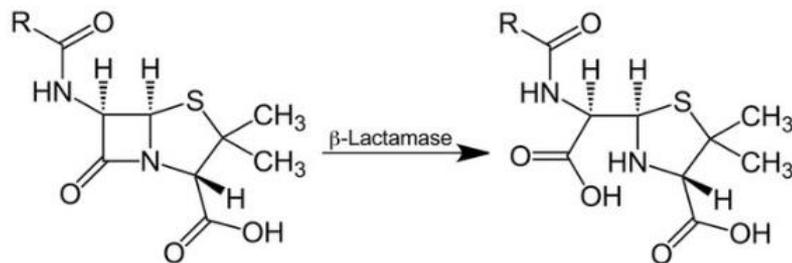
Statens Serum Institut

- ❖ *S. aureus*: Opportunistic pathogen in humans and animals
- ❖  $\beta$ -lactams including penicillins and cephalosporins used since the early 1940s and late 1950s, respectively
- ❖ Bind to and inactivate the transpeptidase domain of native PBPs involved in cell wall synthesis



## Penicillin resistance

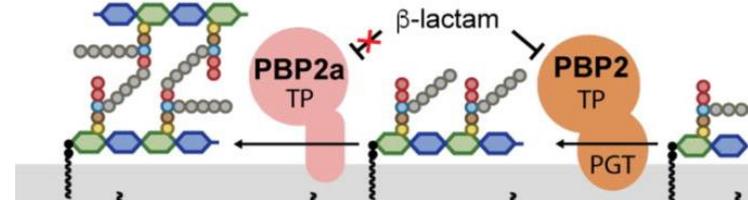
- ❖ *blaZ*
- ❖ Usually plasmid-borne
- ❖ Penicillinase
- ❖ Enzymatic cleavage of the  $\beta$ -lactam ring in penicillins



[Susann Skagseth](#)

## Methicillin resistance

- ❖ *mecA* or *mecC*
- ❖ Present on SCC*mec*
- ❖ PBP2a or PBP2c
- ❖ Low affinity for penicillins and cephalosporins



Modified from: J Am Chem Soc. 2017 Jul 26; 139(29): 9791–9794

## THE LANCET Infectious Diseases

Volume 11, Issue 8, August 2011, Pages 595-603



Fast track — Articles

Meticillin-resistant *Staphylococcus aureus* with a novel *mecA* homologue in human and bovine populations in the UK and Denmark: a descriptive study

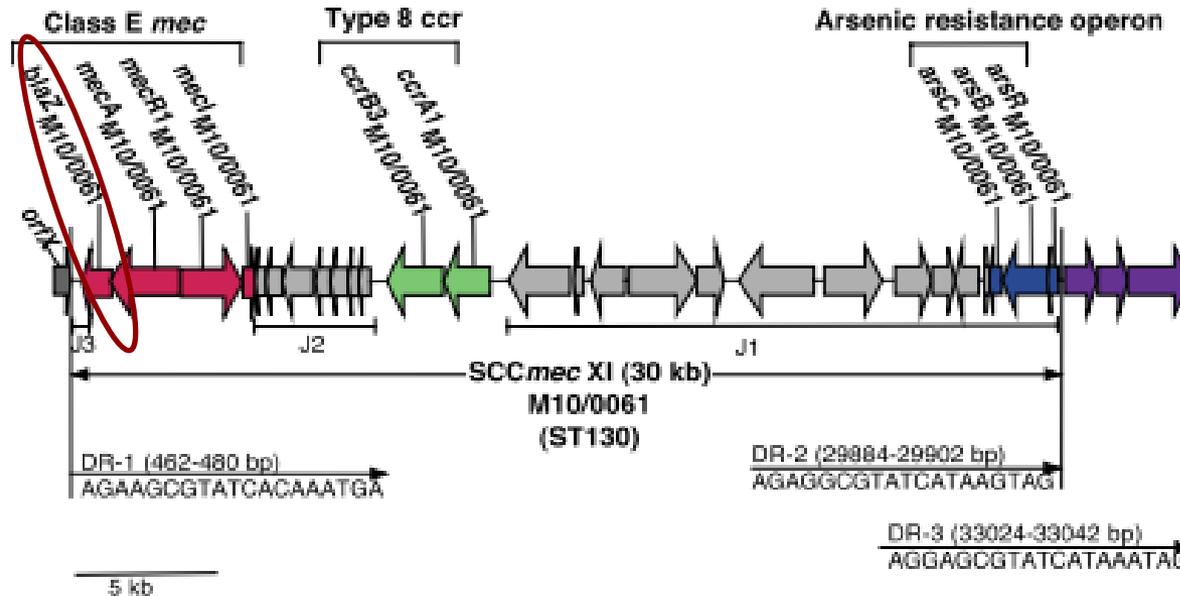
Laura García-Álvarez PhD <sup>a</sup>, Matthew TG Holden PhD <sup>b</sup>, Heather Lindsay BSc <sup>a</sup>, Cerian R Webb PhD <sup>a</sup>, Derek FJ Brown PhD <sup>c</sup>, Martin D Curran PhD <sup>c</sup>, Enid Walpole FIMLS <sup>c</sup>, Karen Brooks BSc <sup>b</sup>, Derek J Pickard PhD <sup>b</sup>, Christopher Teale MRCVS <sup>d</sup>, Prof Julian Parkhill PhD <sup>b</sup>, Stephen D Bentley PhD <sup>b</sup>, Giles F Edwards FRCPath <sup>e</sup>, E Kirsty Girvan MSc <sup>e</sup>, Angela M Kearns PhD <sup>f</sup>, Bruno Pichon PhD <sup>f</sup>, Robert LR Hill PhD <sup>f</sup>, Anders Rhod Larsen PhD <sup>g</sup> ... Dr Mark A Holmes VetMB <sup>a</sup>,  

2011:

- *mecC*- MRSA isolated from a milk sample in the UK and in human cases in Denmark
- low prevalence in dairy cows, and in 1-3% of human MRSA infections in Denmark

García-Álvarez et al. *Lancet Infect. Dis.* **11**, 595-603 (2011)  
Shore et al. *Antimicrob. Agents Chemother.* **55**, 3765-3773 (2011)  
Harrison et al. *EMBO Mol. Med.* **5**, 509-515 (2013)  
Paterson et al. *Trends Microbiol.* **22**, 42-47 (2014)  
DANMAP 2020 (2021)

- Novel *mecA*-homologue (*mecA*<sub>LGA251</sub> later *mecC*)
- 30 Kb SCC*mec* XI

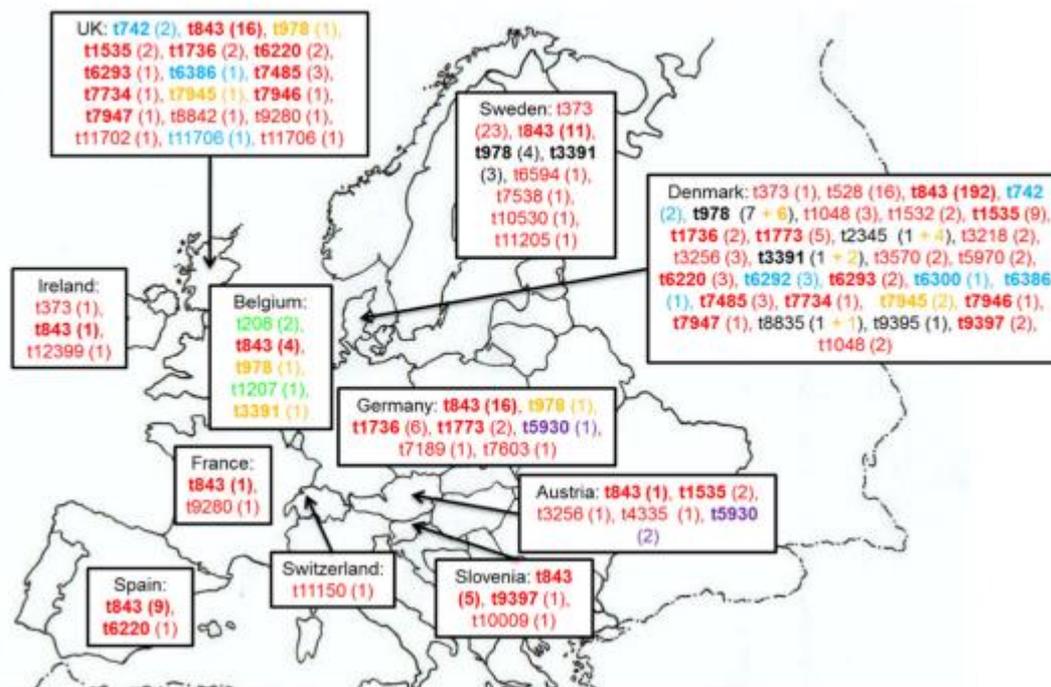


Shore et al. *Antimicrob. Agents Chemother.* **55**, 3765-3773 (2011)  
García-Álvarez et al. *Lancet Infect. Dis.* **11**, 595-603 (2011)

PBP2c shares 70% homology with PBP2a

- ❖ PBP2c: higher affinity for oxacillin than for cefoxitin
- ❖ *mecC*-MRSA: frequently **FOX<sup>R</sup>-OXA<sup>S</sup>**
- ❖ **Cefoxitin** is a better predictor for *mecC* MRSA than oxacillin
  - PBP2c: thermosensible
    - OXA<sup>S</sup> at 37 °C
    - OXA<sup>R</sup> at 22 °C
- ❖ Generally **susceptible** to non  $\beta$ - lactams

• Most strains belong to **CC130**, **CC425** and **CC1943**



- ∴ Dairy cows were considered to be the most likely reservoir with transmission from livestock to humans
- ∴  $\beta$ -lactams are commonly used to treat bovine mastitis



.. but *mecC* MRSA are also found in wildlife (low frequency )

Recently found to be widespread in Scandinavian hedgehogs (60-65%)

Bengtsson et al. *Vet. Microbiol.* **207**, 203-207 (2017)  
Rasmussen et al. *PLoS One* **14**, e0222031 (2019)



Are hedgehogs a natural host of *mecC*-MRSA in other countries?



Why are *S. aureus* on hedgehogs resistant towards methicillin?



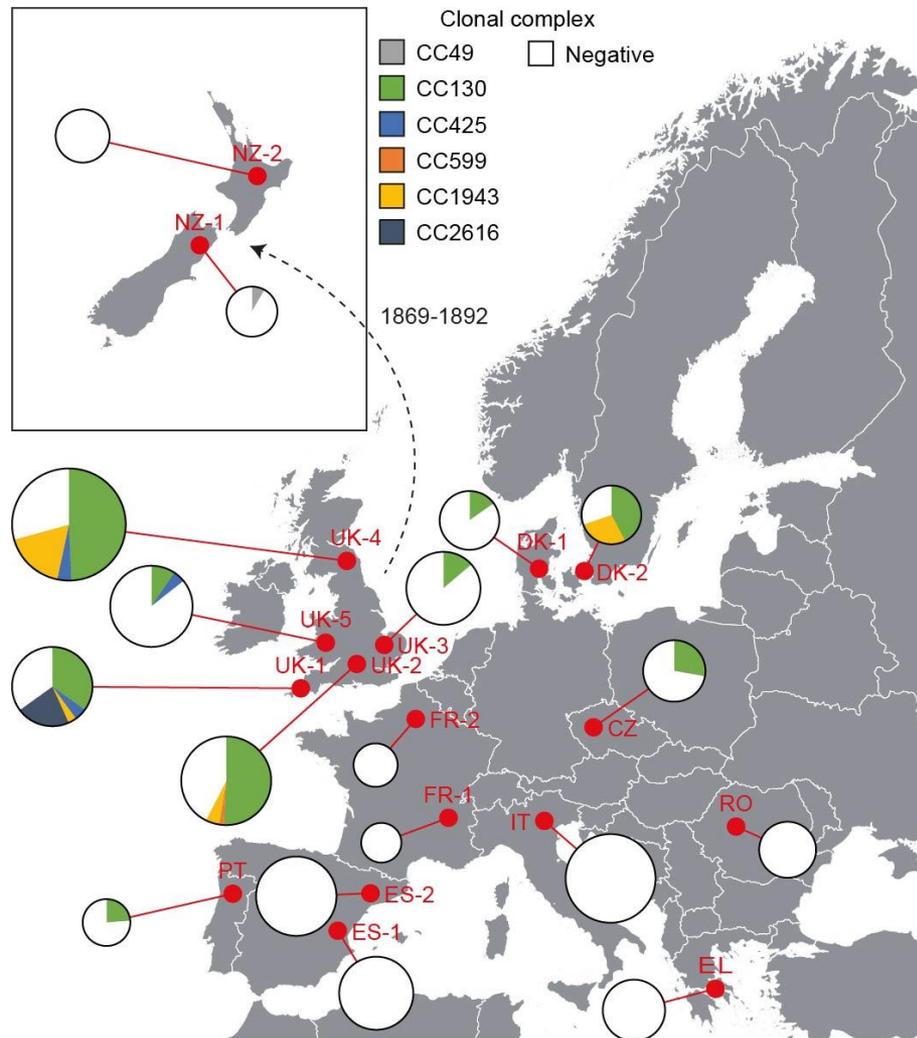
What is the role of hedgehogs in the epidemiology/evolution of *mecC*-MRSA?



- ❖ 16 wildlife rescue centres in 10 European countries
- ❖ 2 wildlife rescue centres in New Zealand
- ❖ 276 hedgehogs = 828 samples (nasal area, skin and feet)



# *mecC* MRSA in European hedgehogs



844

NATURE

February 22, 1964 VOL. 201

delay and the same abnormal phylotaxy. However, its embryonic structure made no progress in the two years in spite of the apical position on the shoot system. As it was necessary to remove all the large expanding buds, this GA<sub>1</sub> formation might be connected with the small buds known and is frequently observed to occur in *Pinus peledis*. The isolates were phage typed and their antibiotic sensitivities were investigated. Approximately 90 per cent of the isolates could be tested single because *Staphylococcus aureus* strains were used.

Dermatophytes are known to produce antibiotics and penicillin has been isolated from *T. mentagrophytes*<sup>3</sup>. The hedgehog variant of this species *in vitro* can be shown to produce considerable quantities of a penicillin-like substance, inhibitory to sensitive *Staphylococci* and neutralized by penicillinase. The type strain of the variant *IMI. 101.051* and 3 other isolates were grown in Sabouraud broth shake cultures for 5 days. The filtrates of all produced zones of inhibition equivalent to 1.5 units/ml. of penicillin in plates seeded with the Oxford strain of *Staphylococcus aureus*. Addition of penicillinase to the filtrates destroyed their inhibitory powers.

skin surface and pass of 63 per cent and 71 per cent, respectively. It was noticeable that areas of skin carrying the dermatophyte yielded large numbers of non-glucose-positive *Staphylococci* in almost pure culture. This colonization of mycotic lesions by pathogenic *Staphylococci* is well known from otitis media with clinical lesions. PLDH determinations were made according to the method of Berger and Benda, using reagents obtained from Sigma Chemical Co. Plasma samples were obtained using 0.1 ml. of a 50 mg/ml. solution of sterile heparin.

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Smith & Marples. *Nature* 201, 844 (1964)

- Dermatophyte, opportunistic pathogen in hedgehogs (ringworm)
  - and in dogs with secondary transmission to humans



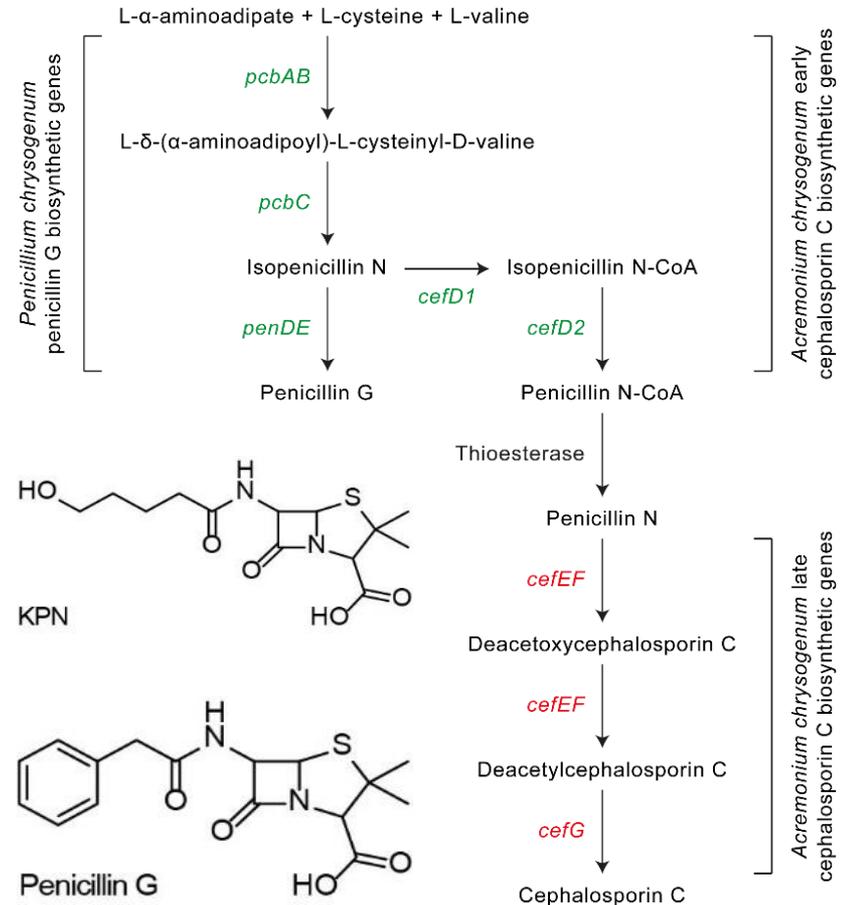
- Common in West European hedgehogs (*Erineceus europaeus*)



# Production of penicillins in *Trichophyton erinacei*

Genome  
sequencing  
and search for  
 $\beta$ -lactam  
biosynthetic  
genes

Search for  $\beta$ -  
lactams using  
LC-MS and  
molecular  
networking  
analysis



RESEARCH

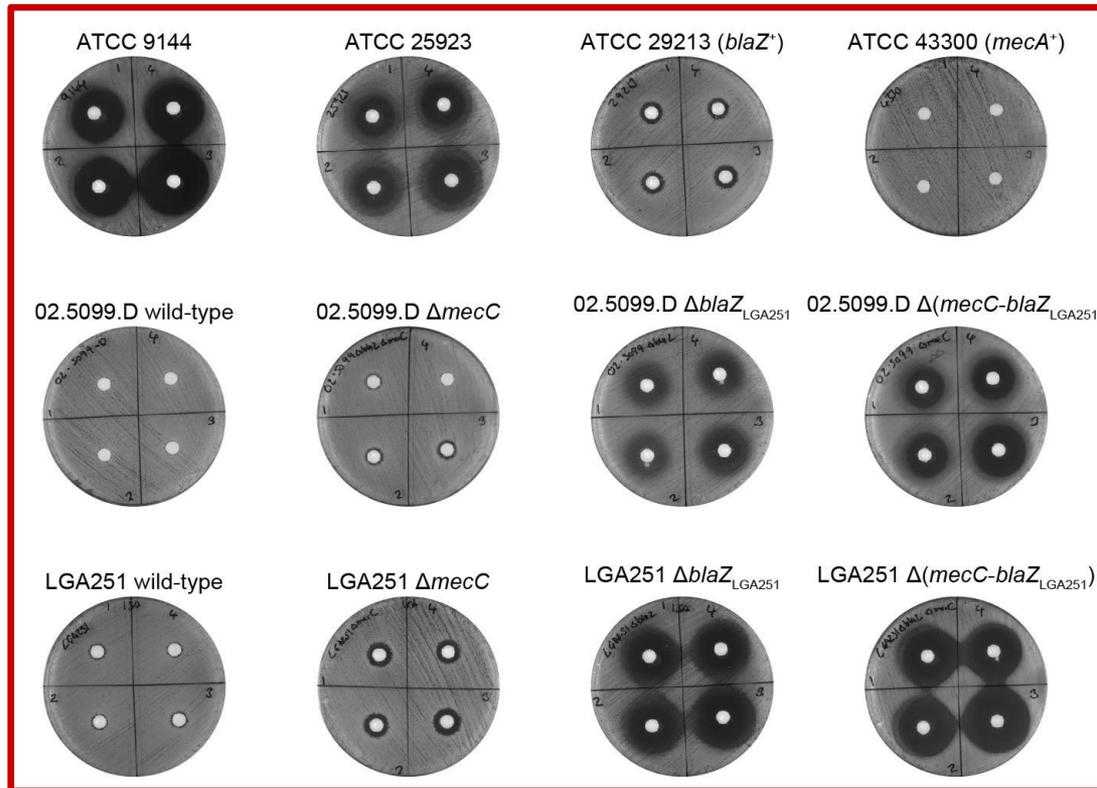
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# Benzylopenicillin-producing *Trichophyton erinacei* and methicillin resistant *Staphylococcus aureus* carrying the *mecC* gene on European hedgehogs – A pilot-study



Faruk Dube<sup>1,2\*</sup>, Robert Söderlund<sup>2</sup>, Matilda Lampinen Salomonsson<sup>3,4</sup>, Karin Troell<sup>2,5</sup> and Stefan Börjesson<sup>6,7</sup>

# Activity of penicillins produced by *T. Erinacei*



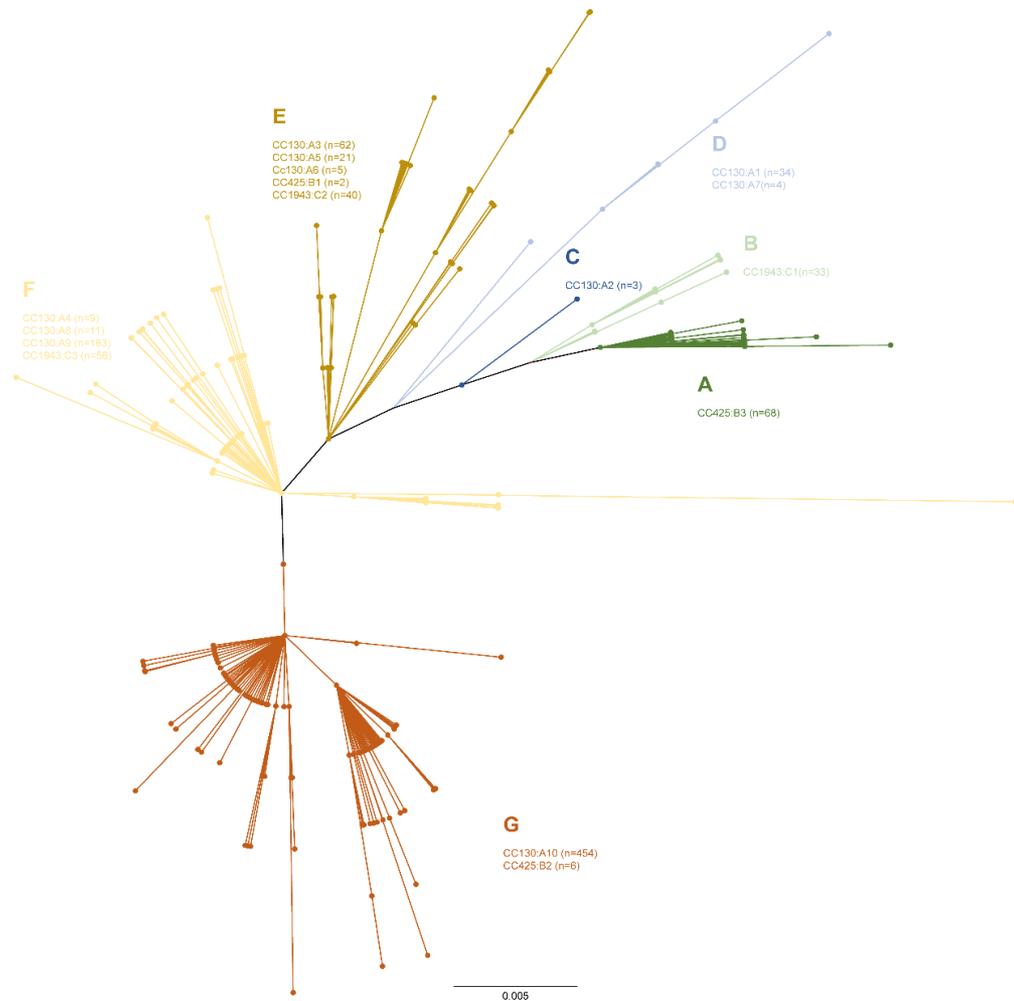
- ❖ WGS of CC130, CC425 and CC1943
  - 205 *mecC*-MRSA and 9 MSSA isolates from hedgehogs
  - 786 *mecC*-MRSA and 127 MSSA isolates from other sources (mainly humans, cattle, sheep, goats and wild animals from western and central Europe)



# Several introductions of SCCmec XI

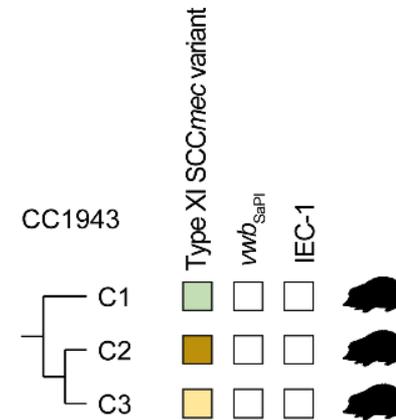
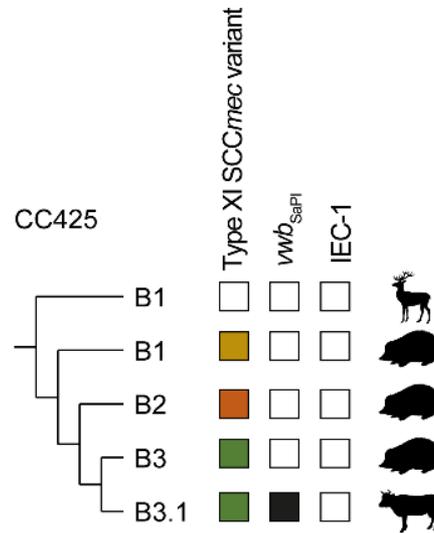
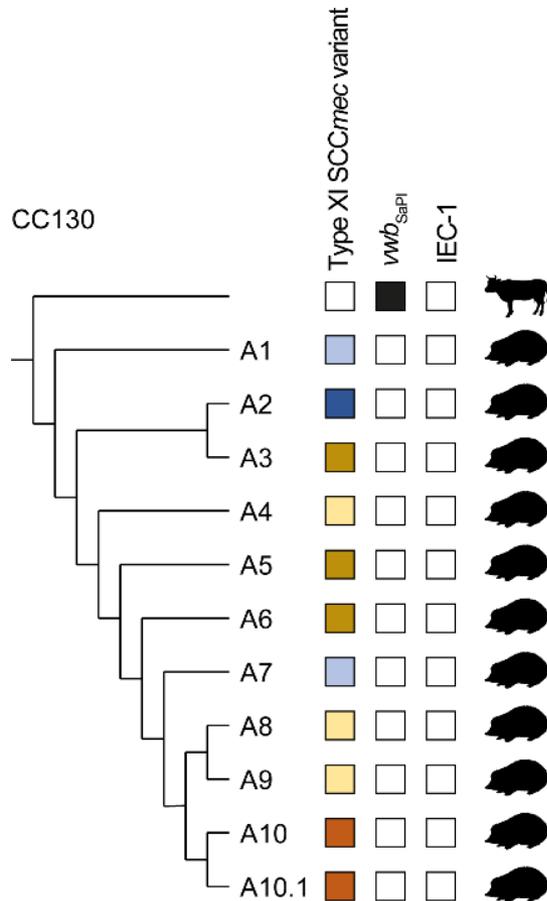
Phylogenetic  
analysis of  
SCCmec XI  
(n=991)

SCCmec XI in  
16  
monophyletic  
lineages

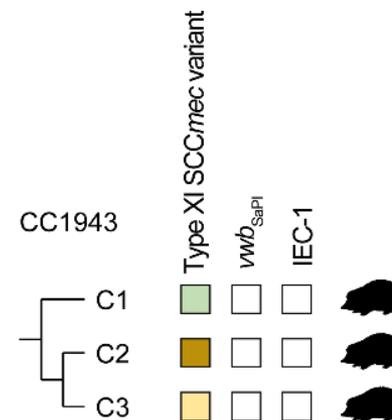
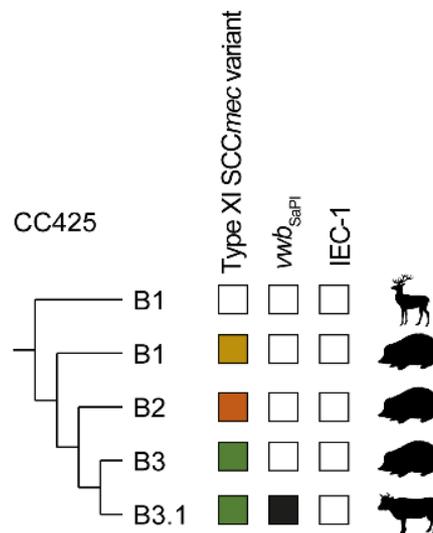
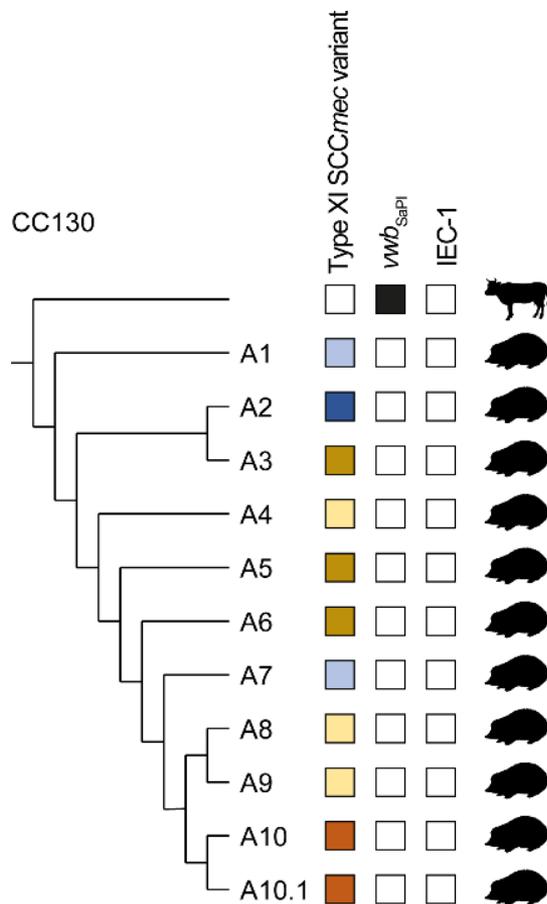


- Genetic markers of host adaptation
  - IEC-1 → evasion of the human innate immune response (0%)
  - $vwb_{\text{SaPI}}$  → von Willebrand factor with coagulase activity against ruminant plasma (4%)



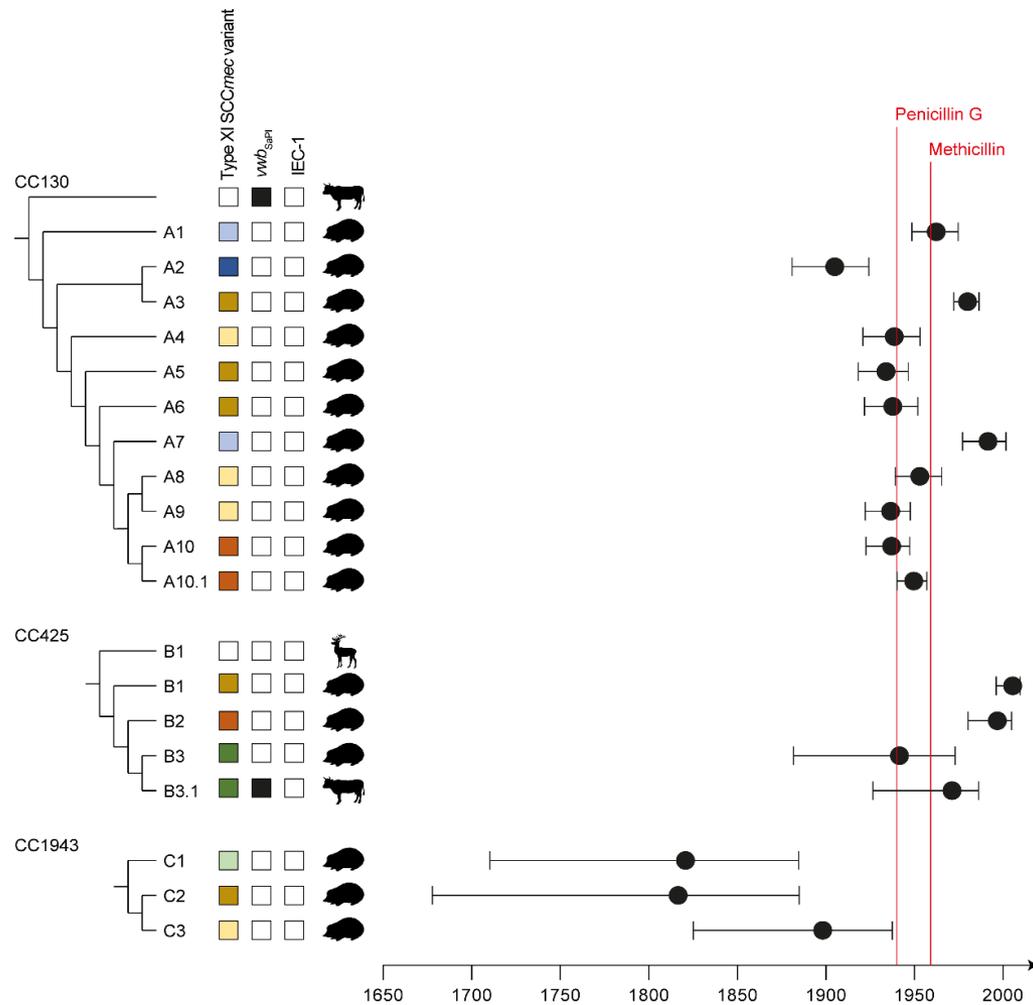


Hedgehogs are host in all evolutionary lineages



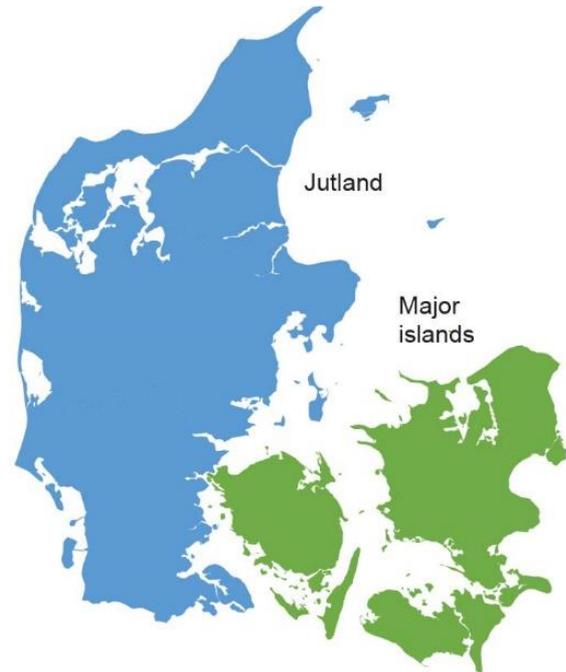
How old are the different *mecC*-MRSA lineages?

# Time scaled analysis (SNP and isolation date)

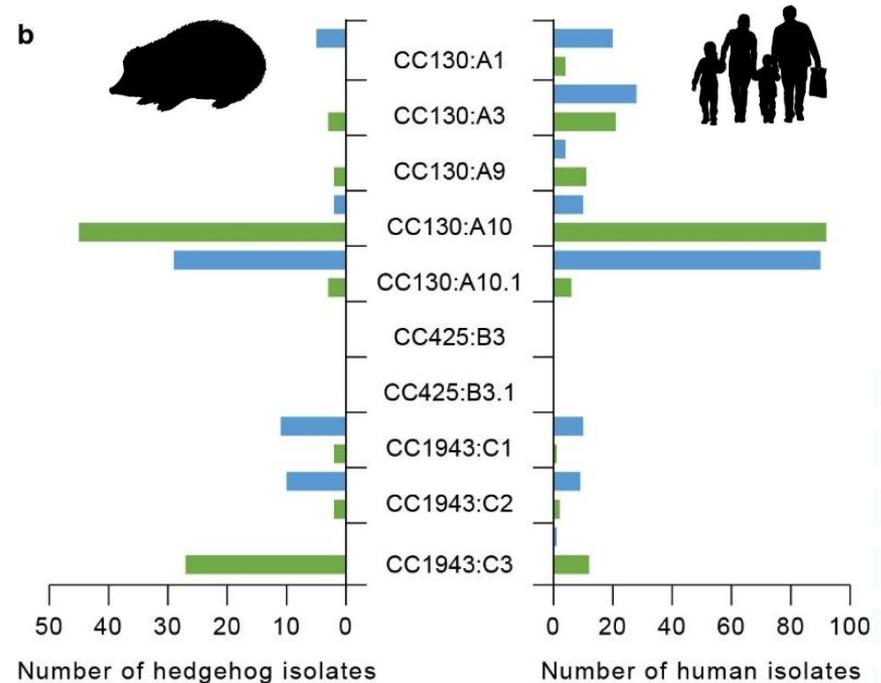
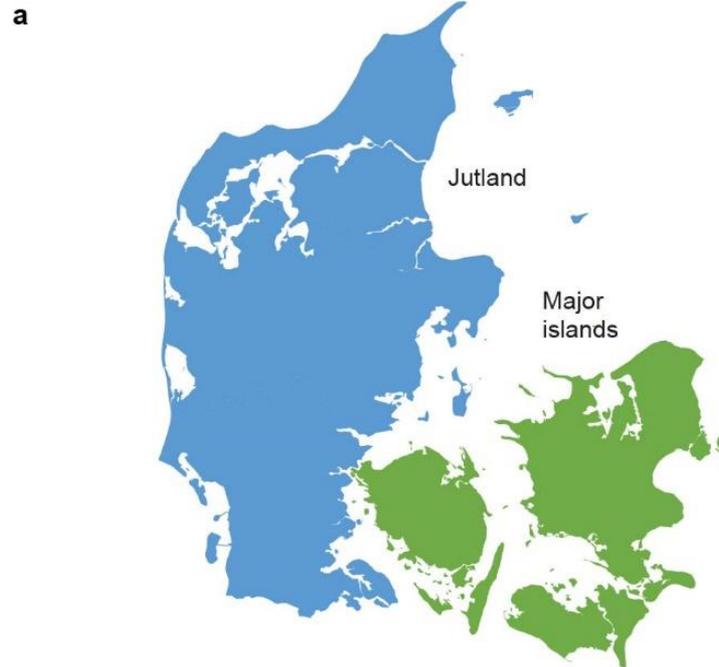


- Hedgehogs have a limited capacity for dispersal over long distances (3-4 km) and between islands
- Two Danish hedgehog subpopulations
  - Jutland (peninsula connected to Europe)
  - Major islands

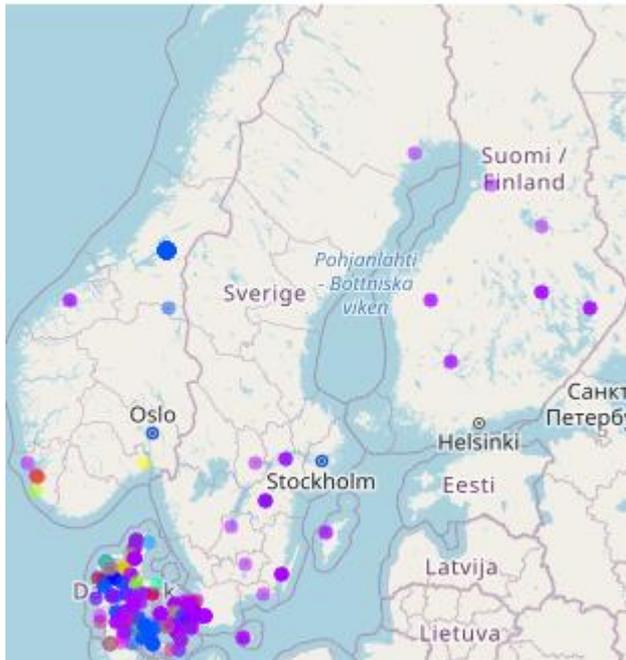
a



- Distribution of *mecC* MRSA subtypes are strikingly similar in hedgehog and human populations



- Northern border of human CC130 MRSA cases resembles the distribution of hedgehogs



## Distribution of the European hedgehog (*Erinaceus europaeus* L.) in Sweden and Finland

Hans Kristiansson

Kristiansson, H. 1981: Distribution of the European hedgehog (*Erinaceus europaeus* L.) in Sweden and Finland. — *Ann. Zool. Fennici* 18: 115—119.

Information on the distribution and changes in abundance of the hedgehog in Sweden was collected by means of questionnaires. The investigation showed that man has influenced the distribution of the hedgehog in Sweden (as in Finland and Norway) due to intentional introduction. In Finland and Sweden, its range has expanded during the twentieth century. However, this has occurred much faster in Finland than in Sweden. At present, the hedgehog is found in most parts of southern and central Sweden, and in Norrland, along the coast up to the Finnish border.

A "minimum time-span" was calculated to predict the areas in which the hedgehog is expected to be found in self-maintained populations. This time-span was calculated to 155 days and covers the time needed for reproduction, storage of energy and growth of the young. It corresponds rather well with the northern distribution limit of the hedgehog. It was found that no large-scale general changes in abundance occurred between 1975 and 1979.

*Hans Kristiansson, Department of Animal Ecology, University of Lund, Ecology Building, S-223 62 Lund, Sweden.*

<https://nrar.shinyapps.io/nordicmrna/>

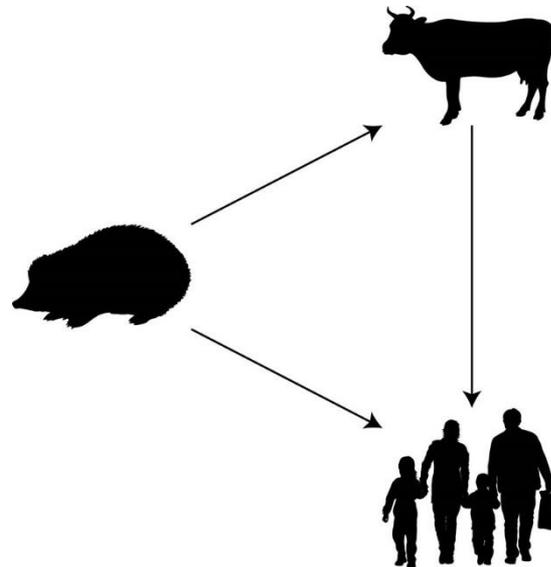
- Hedgehogs are the most likely primary host of *mecC*-MRSA
- Human *mecC*-MRSA isolates probably originate from local hedgehog reservoirs



- ❖ Methicillin resistance in *S. aureus* emerged in the pre-antibiotic era as a co-evolutionary adaptation to the colonization of dermatophyte-infected hedgehogs



- Subsequently, these *mecC*-MRSA lineages have spread within the local hedgehog populations and between hedgehogs and secondary hosts, including livestock and humans



- ❖ The evolution of resistance genes in natural environments demonstrates that the use of a One Health approach is critical for our understanding and management of antibiotic resistance



## Article

# Emergence of methicillin resistance predates the clinical use of antibiotics

<https://doi.org/10.1038/s41586-021-04265-w>

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Jesper Larsen<sup>1,55</sup>✉, Claire L. Raisen<sup>2,55</sup>, Xiaoliang Ba<sup>2</sup>, Nicholas J. Sadgrove<sup>3</sup>, Guillermo F. Padilla-González<sup>3</sup>, Monique S. J. Simmonds<sup>3</sup>, Igor Loncaric<sup>4</sup>, Heidrun Kerschner<sup>5</sup>, Petra Apfalter<sup>5</sup>, Rainer Hartl<sup>5</sup>, Ariane Deplano<sup>6</sup>, Stien Vandendriessche<sup>6,46</sup>, Barbora Černá Bolfíková<sup>7</sup>, Pavel Hulva<sup>8,9</sup>, Maiken C. Arendrup<sup>1</sup>, Rasmus K. Hare<sup>1</sup>, Céline Barnadas<sup>1,10</sup>, Marc Stegger<sup>1</sup>, Raphael N. Sieber<sup>1</sup>, Robert L. Skov<sup>11</sup>, Andreas Petersen<sup>1</sup>, Øystein Angen<sup>1</sup>, Sophie L. Rasmussen<sup>12,13</sup>, Carmen Espinosa-Gongora<sup>14</sup>, Frank M. Aarestrup<sup>15</sup>, Laura J. Lindholm<sup>16</sup>, Suvi M. Nykäsenoja<sup>17</sup>, Frederic Laurent<sup>18</sup>, Karsten Becker<sup>19</sup>, Birgit Walther<sup>20,47</sup>, Corinna Kehrenberg<sup>21</sup>, Christiane Cuny<sup>22</sup>, Franziska Layer<sup>22</sup>, Guido Werner<sup>22</sup>, Wolfgang Witte<sup>22</sup>, Ivonne Stamm<sup>23</sup>, Paolo Moroni<sup>24,48</sup>, Hannah J. Jørgensen<sup>25</sup>, Hermínia de Lencastre<sup>26,27</sup>, Emilia Cercenado<sup>28</sup>, Fernando García-Garrote<sup>28,49</sup>, Stefan Börjesson<sup>29,50</sup>, Sara Hæggman<sup>30</sup>, Vincent Perreten<sup>31</sup>, Christopher J. Teale<sup>32</sup>, Andrew S. Waller<sup>33,51,52</sup>, Bruno Pichon<sup>34</sup>, Martin D. Curran<sup>35</sup>, Matthew J. Ellington<sup>35,53</sup>, John J. Welch<sup>36</sup>, Sharon J. Peacock<sup>37</sup>, David J. Seilly<sup>2</sup>, Fiona J. E. Morgan<sup>2,54</sup>, Julian Parkhill<sup>2</sup>, Nazreen F. Hadjirin<sup>2</sup>, Jodi A. Lindsay<sup>38</sup>, Matthew T. G. Holden<sup>39</sup>, Giles F. Edwards<sup>40</sup>, Geoffrey Foster<sup>41</sup>, Gavin K. Paterson<sup>42</sup>, Xavier Didelot<sup>43</sup>, Mark A. Holmes<sup>2,56</sup>, Ewan M. Harrison<sup>37,44,45,56</sup> & Anders R. Larsen<sup>1,56</sup>

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## All the authors, especially:

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## Other contributors

- ❖ Staff members of the wildlife rescue centres
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