Diphtheria is a contagious, potentially fatal infection caused by toxin-producing bacteria of the Corynebacterium diphtheriae species complex, which includes C. diphtheriae, C. ulcerans, C. pseudotuberculosis, C. rouxii, C. belfantii, and C. silvaticum. Infection is localized principally in the upper respiratory tract, and production of diphtheria toxin (encoded by the tox gene) can cause systemic complications. Cutaneous diphtheria and diphtheria endocarditis can also act as sources of respiratory infections (1–4). Diphtheria surveillance has traditionally focused on respiratory illness caused by toxigenic C. diphtheriae but has been expanded in some countries to include all C. diphtheriae species complex infections irrespective of species, infection site, or toxigenicity, enabling broader disease monitoring. C. diphtheriae spreads via human-to-human contact; C. ulcerans and C. pseudotuberculosis are transmitted to humans primarily through animal contact. Diphtheria was once a major cause of infant death, but global incidence has declined over the past century, largely because of mass vaccination. Consequently, diphtheria is now often considered a forgotten disease (5). Nevertheless, diphtheria reemergence has been reported in high-income countries and is closely related to patient travel history. Diphtheria is considered endemic in Madagascar, Comoros, and Mayotte in the southwest Indian Ocean, but few cases have been reported on other islands, including Réunion Island, an overseas department of France, where cases emerged in 2015 (6,7). Vaccination coverage is poorer in Mayotte (45% for 7- to 11-year-old children) than in Réunion Island (96% for children 11 months of age). Recent improvements in laboratory diagnostic capabilities, such as mass spectrometry use, have increased reports of C. diphtheriae species complex infections (8). However, knowledge of prevalence and origin of those infections is limited in this region. The aims of this study were to review the clinical, epidemiologic, and microbiologic characteristics of C. diphtheriae species complex infections on Réunion Island, France, during 2015–2020. Isolates were genetically diverse, indicating circulation and local transmission of several diphtheria sublineages. Clinicians should remain aware of the risk for diphtheria and improve diagnostic methods and patient management.

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Réunion Island during 2015–2020 and identify possible links with cases on other islands in the region.

**The Study**

We included all cases of *C. diphtheriae* species complex infections reported to the regional health agency and recorded at Réunion Island University Hospital during 2015–2020. We analyzed medical records and extracted age, sex, country of residence, recent travel, contact with animals, socioeconomic status, and diphtheria vaccination status for each case. We performed antimicrobial susceptibility testing; identified co-infecting strains; and determined tox gene presence, diphtheria toxin production, and biovar and sequence type (ST). We sent each isolate to the National Reference Center for Corynebacteria of the diphtheriae Complex (Institut Pasteur, Paris, France) to confirm species identity through multiplex PCR and biotyping as previously described (8–10). We detected the tox gene by using conventional PCR or, since 2019, by using multiplex real-time PCR (10). We assessed toxin production by using a modified Elek test (11). We determined antimicrobial drug susceptibility by using disk diffusion or by determining MICs (E-test; bioMérieux, https://www.biomerieux.com), in accordance with CASFM/EUCAST2021 (https://www.sfm-microbiologie.org/2021/04/23/casfm—avril-2021-v1-0) recommendations for benzylpenicillin, amoxicillin, cefotaxime, clindamycin, rifampin, and ciprofloxacin. We genotyped each isolate by using multilocus sequence typing (MLST) (12).

A total of 26 cases of *C. diphtheriae* species complex infections were recorded, from which 27 *C. diphtheriae* and 2 *C. ulcerans* isolates were cultured. Most (88.5%) infected patients were male; median age was 60 (interquartile range 32.5–67) years. Fourteen (50%) patients lived on Réunion Island, 3 (11.5%) in Mayotte, 4 (19.2%) in mainland France, 3 (11.5%) in Comoros, and 2 (7.8%) in Madagascar. Most (84.6%) patients had skin manifestations, and 16 patients were vaccinated (Table 1, https://wwwnc.cdc.gov/EID/article/29/8/23-0106-T1.htm; Appendix Figure, https://wwwnc.cdc.gov/EID/article/29/8/23-0106.pdf). Of 24 *C. diphtheriae* infections, 8 occurred in patients who had recently traveled to or originated from Madagascar, 4 who traveled to or originated from Mayotte, and 3 who traveled to or originated from Comoros. Since 2018, a total of 9 cases on Réunion Island have been considered locally acquired; all of those patients lived in poor socioeconomic conditions. *C. ulcerans* infections occurred in 2 patients living on Réunion Island who had not traveled recently but had contact with animals (Table 1; Figure). We performed a Spearman rank correlation to compare locally acquired strains isolated during 2015–2018 and 2019–2020; a 75% increase in locally acquired *C. diphtheriae* infections occurred in 2019–2020 (ρ = 0.8452; p = 0.0341).

Isolates were obtained from cutaneous lesion (n = 24), bone (n = 4), and respiratory (n = 1) samples. Eight of 27 *C. diphtheriae* isolates were toxigenic, yielding positive Elek test results. The 2 *C. ulcerans* isolates were nontoxigenic. *C. diphtheriae* isolates were characterized as biovars Mitis (n = 20) and Gravis (n = 7). Patient isolates were co-infected most frequently with *Staphylococcus aureus* (n = 17) and *Streptococcus pyogenes* (n = 18). Benzylpenicillin resistance was observed in 80% of isolates according to CASFM/EUCAST2021 recommendations, but isolates were categorized as susceptible increased exposure according to EUCAST version 13.0 proposed breakpoints (https://www.eucast.org/clinical_breakpoints) (Appendix Table). One (3.5%) *C. diphtheriae* isolate was resistant to amoxicillin (CD8/FRC0402; MIC 1.5 mg/L).

**Figure.** Number of cases diagnosed per year in study of emerging *Corynebacterium diphtheriae* species complex infections, Réunion Island, France, 2015–2020. Number of cases were classified according to geographic origin (A) or travel history of patients (B). Dotted lines indicate linear trends.
and 1 was resistant to rifampin. Both C. ulcers iso-
lates were resistant to clindamycin (100%, natural low
susceptibility), whereas clindamycin resistance was
observed for only 1 C. diphtheriae isolate.

We identified 21 STs by MLST analysis, includ-
ing ST88 for C. diphtheriae isolates from 4 patients and
ST339 for both C. ulcers isolates (Table 2). All C.
diphtheriae STs had 2–5 mismatches, except ST87 and
ST237, which had 1 mismatch between them. ST339 (C.
ulcers) had 7 mismatches with all C. diphtheriae STs.

Conclusions
We report increased prevalence of cutaneous C. diphthe-
riae species complex infections on Réunion Island during
2015–2020. Introduction of mass spectrometry analysis
in hospital laboratories and increased clinician aware-
ness might have led to increased case reporting. Our
study confirms that C. diphtheriae species complex mem-
bers are circulating and are likely underestimated in the
southwest Indian Ocean (7,13). Moreover, we observed
emergence of locally acquired cutaneous C. diphtheriae
infections on Réunion Island since 2019. The number of
imported cases in 2020 was probably limited because of
the COVID-19 pandemic, which reduced travel. Indeed,
all C. diphtheriae cases identified during 2015–2018 oc-
curred in patients who had traveled from other islands
in the Indian Ocean. In addition, cutaneous diphtheria
appeared to be associated with poor socioeconomic liv-
ing conditions, in which alcoholism, drug dependence,
and homelessness are factors that increase risk for hu-
man-to-human transmission and virulence (14).

A total of 8 (30%) C. diphtheriae isolates were tox-
genic and caused cutaneous infections. Nontoxigenic
C. diphtheriae isolates (70%, n = 19) were obtained
from cutaneous lesions, respiratory samples, and bone
samples. Clinicians should be aware that nontoxigenic
C. diphtheriae can potentially cause severe disease
(1,14,15). Moreover, all isolates were co-infected with
pyogenic bacteria, suggesting diphtheria infection
should be considered under polymicrobial conditions.

MLST analysis identified 21 different STs; most
were unrelated (>2 mismatches) reflecting marked

Table 2. Characteristics of isolates from 26 patients in study of emerging Corynebacterium diphtheriae species complex infections, Réunion Island, France, 2015–2020*

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Isolate</th>
<th>Year</th>
<th>Isolation site</th>
<th>Species</th>
<th>Biovar</th>
<th>tox gene</th>
<th>Elek test</th>
<th>ST†</th>
<th>Co-infections‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD1/FRC0304</td>
<td>2015</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Gravis</td>
<td>Negative</td>
<td>NA</td>
<td>102</td>
<td>S. pyogenes, S. aureus, A. haemolyticum</td>
</tr>
<tr>
<td>2</td>
<td>CD2/FRC0316</td>
<td>2015</td>
<td>Respiratory</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>95</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>3</td>
<td>CD3/FRC0314</td>
<td>2015</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Positive</td>
<td>Positive</td>
<td>421</td>
<td>S. aureus</td>
</tr>
<tr>
<td>4</td>
<td>CD4/FRC0376</td>
<td>2015</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Gravis</td>
<td>Positive</td>
<td>Positive</td>
<td>388</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>5</td>
<td>CD5/FRC0383</td>
<td>2015</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>423</td>
<td>S. pyogenes, S. aureus</td>
</tr>
<tr>
<td>6</td>
<td>CD6/FRC0393</td>
<td>2015</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>423</td>
<td>S. pyogenes, S. aureus</td>
</tr>
<tr>
<td>7</td>
<td>CD7/FRC0385</td>
<td>2015</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Positive</td>
<td>Positive</td>
<td>91</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>8</td>
<td>CD8/FRC0391</td>
<td>2015</td>
<td>Cutaneous</td>
<td>C. ulcerans</td>
<td>NA</td>
<td>Negative</td>
<td>NA</td>
<td>339</td>
<td>S. dysgalactiae</td>
</tr>
<tr>
<td>9</td>
<td>CD9/FRC0410</td>
<td>2015</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>410</td>
<td>S. dysgalactiae</td>
</tr>
<tr>
<td>10</td>
<td>CD10/FRC0423</td>
<td>2015</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>415</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>12</td>
<td>CD12/FRC0501</td>
<td>2015</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Gravis</td>
<td>Positive</td>
<td>Positive</td>
<td>521</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>13</td>
<td>CD13/FRC0624</td>
<td>2018</td>
<td>Bone</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>237</td>
<td>S. aureus</td>
</tr>
<tr>
<td>14</td>
<td>CD14/FRC0630</td>
<td>2018</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Gravis</td>
<td>Negative</td>
<td>NA</td>
<td>606</td>
<td>S. pyogenes, S. aureus</td>
</tr>
<tr>
<td>15</td>
<td>CD15/FRC0733</td>
<td>2019</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Gravis</td>
<td>Negative</td>
<td>NA</td>
<td>351</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>16</td>
<td>CD16/FRC0782</td>
<td>2019</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Positive</td>
<td>Positive</td>
<td>688</td>
<td>S. pyogenes, S. aureus</td>
</tr>
<tr>
<td>17</td>
<td>CD17/FRC0809</td>
<td>2019</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Gravis</td>
<td>Positive</td>
<td>Positive</td>
<td>688</td>
<td>S. pyogenes, S. aureus</td>
</tr>
<tr>
<td>18</td>
<td>CD18/FRC0819</td>
<td>2019</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Gravis</td>
<td>Positive</td>
<td>Positive</td>
<td>87</td>
<td>S. pyogenes, A. haemolyticum</td>
</tr>
<tr>
<td>19</td>
<td>CD19/FRC0849</td>
<td>2019</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Positive</td>
<td>Positive</td>
<td>426</td>
<td>S. pyogenes, S. aureus</td>
</tr>
<tr>
<td>20</td>
<td>CD20/FRC0865</td>
<td>2020</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>102</td>
<td>S. pyogenes, S. aureus</td>
</tr>
<tr>
<td>21</td>
<td>CD21/FRC0875</td>
<td>2020</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>707</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>22</td>
<td>CD22/FRC0893</td>
<td>2020</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>708</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>23</td>
<td>CD23/FRC0928</td>
<td>2020</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>88</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>24</td>
<td>CD24/FRC0970</td>
<td>2020</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>88</td>
<td>S. pyogenes, S. aureus, A. haemolyticum</td>
</tr>
<tr>
<td>25</td>
<td>CD25/FRC0975</td>
<td>2020</td>
<td>Cutaneous</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>88</td>
<td>S. aureus</td>
</tr>
<tr>
<td>26</td>
<td>CD26/FRC1050</td>
<td>2020</td>
<td>Bone</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>771</td>
<td>A. haemolyticum</td>
</tr>
<tr>
<td>27</td>
<td>CD27/FRC1065</td>
<td>2020</td>
<td>Bone</td>
<td>C. diphtheriae</td>
<td>Mitis</td>
<td>Negative</td>
<td>NA</td>
<td>88</td>
<td>S. aureus</td>
</tr>
</tbody>
</table>

*CD, Corynebacterium diphtheriae; CU, C. ulcers; NA, not applicable; ST, sequence type.
†Numbers in bold indicate a common ST shared among strains from different patients.
‡Co-infections with Arcanobacterium haemolyticum, Staphylococcus aureus, Streptococcus dysgalactiae, or Streptococcus pyogenes.
genetic diversity of isolates. ST88 was found in 4 patients living on Réunion Island who had not traveled recently, indicating probable local acquisition. ST88 had previously been reported only in patients from Mayotte. Therefore, our results show that multiple *C. diphtheriae* species complex clones are circulating in the southwest Indian Ocean (8). Both *C. ulcerans* ST found in animals in France. Although considerable ST diversity was revealed, whole-genome sequencing will be required to further evaluate circulating *C. ulcerans* ST in this region.

In conclusion, we describe emergence of locally acquired *C. diphtheriae* species complex infections on Réunion Island during 2019–2020. Local clinicians and microbiologists should remain aware of this neglected infection; improvements should be made in diagnostic methods and management of infected patients, such as maintaining availability of diphtheria antitoxin.

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### About the Author

Dr. Garrigos is a research scientist in the microbiology department of Félix Guyon University Hospital of Réunion Island, France. His research interests focus on bacterial diseases, antimicrobial resistance, cystic fibrosis patients, and emerging infectious diseases.

### References


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