**Supplementary Appendix**

**Supplementary Appendix 1. Structuring of text data**

Identifying the symptom data (step 1)

Patient narratives were divided according to sentence structures. Sentence structures were grouped into 40 clusters with a 60% threshold and then classified into main themes. Data in symptom-related clusters were selected from classified sentence structures. Stem sorting was then performed in relation to the terms “initial symptom” and “first symptom,” and terms were ordered according to similarity. In addition, terms corresponding to clinical symptoms were selected from the extracted terms. Selected terms were then converted to MedDRA terms. For each site of infection onset, the terms were separated into symptoms that were specific and already known from medical dictionaries and symptoms that were not already known.

Structuring the symptom data (step 2)

Using the list of clinical symptoms identified in step 1, relevant symptoms were judged to be present if there were matching data in the narrative. Based on that judgment, the description “no symptom” or “symptom (−)” was added to change the symptom present/absent status. A distinction was made between “no symptom” (in which case the description indicates that there was no symptom in the narrative) and “no description” (in which case there was no symptom-related description).

Limiting the data by period

The data processed in step 2 were limited to data from the 28-day period found by counting back from the day the infection became serious (the day admission to hospital or transport to hospital was confirmed). Symptoms that occurred on the day the infection became serious were included among the signs and symptoms of infection.

**Supplementary Table S1.** Signs and symptoms of serious infection reported in ≥1% of cases according to site of infection onset in patients who developed serious infection and who had known onset dates of serious infections

|  |  |  |
| --- | --- | --- |
| Site of infection onset and signs or symptomsa | Previously known as a sign or symptom (yes/no) | Incidence, *n* (%)*N* = 782 patients |
| Respiratory infection |  |  |
| Cough | Yes | 98 (12.5) |
| Pyrexia | Yes | 66 (8.4) |
| Productive cough | Yes | 50 (6.4) |
| Dyspnea | Yes | 36 (4.6) |
| Pain  | No | 27 (3.5) |
| Malaise | Yes | 19 (2.4) |
| Chest pain | No | 17 (2.2) |
| Oropharyngeal pain | Yes | 15 (1.9) |
| Swelling | No | 13 (1.7) |
| Rhinorrhea | Yes | 10 (1.3) |
| Decreased appetite  | No | 9 (1.2) |
| Inflammation  | No | 8 (1.0) |
| Arthralgia | Yes | 8 (1.0) |
| Erythema | No | 8 (1.0) |
| Nasopharyngitis | No | 8 (1.0) |
| Hemoptysis  | No | 8 (1.0) |
| Skin infection |  |  |
| Swelling | No | 57 (7.3) |
| Pain | No | 55 (7.0) |
| Erythema | Yes | 38 (4.9) |
| Rash  | Yes | 23 (2.9) |
| Pyrexia | Yes | 14 (1.8) |
| Feeling hot | No | 12 (1.5) |
| Cough | No | 9 (1.2) |
| Gastrointestinal infection  |  |  |
| Abdominal pain | Yes | 37 (4.7) |
| Pain  | No | 16 (2.0) |
| Diarrhea | Yes | 15 (1.9) |
| Pyrexia | Yes | 11 (1.4) |
| Vomiting | Yes | 9 (1.2) |
| Sepsis |  |  |
| Pyrexia | Yes | 30 (3.8) |
| Pain | No | 17 (2.2) |
| Cough | No | 11 (1.4) |
| Swelling  | No | 11 (1.4) |
| Malaise | Yes | 9 (1.2) |
| Erythema | Yes | 9 (1.2) |
| Vomiting | Yes | 8 (1.0) |
| Urinary tract infection |  |  |
| Vomiting | No | 10 (1.3) |
| Pyrexia | Yes | 9 (1.2) |
| Other infection  |  |  |
| Pain | No | 28 (3.6) |
| Swelling  | No | 23 (2.9) |
| Pyrexia | Yes | 23 (2.9) |
| Erythema | No | 13 (1.7) |
| Arthralgia | Yes | 12 (1.5) |
| Cough | No | 10 (1.3) |
| Back pain | No | 8 (1.0) |

aMedDRA preferred term

**Supplementary Table S2**. Time to onset of serious infection for the most common signs and symptoms of infectiona

|  |  |  |  |
| --- | --- | --- | --- |
| SOC and sign or symptomb | *n*  | Mean (SD) number of days until onset of serious infection | Median number of days until diagnosis of serious infection |
| Gastrointestinal disorders |  |  |  |
| Abdominal pain | 101 | –5.6 (6.5) | –2 |
| Diarrhea | 52 | –4.8 (5.6) | –2 |
| Vomiting | 44 | –4.3 (5.5) | –1 |
| Nausea | 22 | –4.2 (5.0) | –1.5 |
| General disorders and administration site conditions  |  |  |  |
| Pyrexia | 210 | –6.1 (6.2) | –4 |
| Pain | 184 | –6.6 (6.8) | –4 |
| Swelling | 123 | –6.1 (6.1) | –4 |
| Malaise | 63 | –8.7 (7.5) | –5 |
| Inflammation | 39 | –8.8 (6.9) | –7 |
| Feeling hot | 36 | –6.0 (6.7) | –3 |
| Chest pain | 31 | –5.8 (5.8) | –3 |
| Chills | 26 | –4.8 (6.5) | –2 |
| Tenderness | 15 | –8.9 (10.0) | –3 |
| Edema | 15 | –13.5 (9.5) | –14 |
| Feeling abnormal | 13 | –6.0 (7.1) | –2 |
| Asthenia | 11 | –7.2 (8.0) | –5 |
| Infections and infestations |  |  |  |
| Nasopharyngitis | 10 | –5.3 (3.6) | –4.5 |
| Musculoskeletal and connective tissue disorders |  |  |  |
| Arthralgia | 39 | –7.8 (7.5) | –5 |
| Back pain | 23 | –5.6 (6.3) | –3 |
| Arthritis | 15 | –6.3 (7.4) | –4 |
| Joint swelling | 11 | –9.9 (9.6) | –5 |
| Blood and lymphatic system disorders |  |  |  |
| Anemia | 12 | –10.5 (9.6) | –7 |
| Vascular disorders |  |  |  |
| Shock | 11 | –8.1 (9.7) | –2 |
| Hemorrhage | 10 | –8.5 (10.0) | –2 |
| Respiratory, thoracic, and mediastinal disorders |  |  |  |
| Cough | 153 | –6.9 (6.0) | –5 |
| Productive cough | 90 | –6.7 (6.1) | –5 |
| Dyspnea | 65 | –6.5 (6.7) | –3 |
| Oropharyngeal pain | 25 | –6.5 (6.5) | –4 |
| Hemoptysis | 12 | –6.5 (6.0) | –3.5 |
| Rhinorrhea | 11 | –6.3 (5.9) | –4 |
| Nervous system disorders  |  |  |  |
| Depressed level of consciousness | 14 | –8.2 (8.2) | –4 |
| Headache | 10 | –7.7 (6.0) | –6.5 |
| Renal and urinary disorders |  |  |  |
| Glycosuria | 11 | –6.6 (9.0) | –2 |
| Metabolism and nutrition disorder |  |  |  |
| Decreased appetite | 30 | –9.6 (7.4) | –8 |
| Skin and subcutaneous tissue disorders |  |  |  |
| Rash | 77 | –8.6 (7.2) | –6 |
| Erythema | 71 | –5.7 (6.6) | –2 |
| Blister | 12 | –7.8 (5.8) | –6 |
| Skin ulcer | 11 | –9.8 (8.7) | –8 |
| Purpura | 10 | –15.2 (9.0) | –13 |

*SD* standard deviation; *SOC* system order class

aSigns or symptoms with incidences ≥10

bMedDRA preferred term

**Supplementary Table S3** Signs or symptoms of infection that occurred in ≥1% of patients on the day the infection became serious among patients who developed serious infection and who had known onset dates of serious infection

|  |  |
| --- | --- |
| Sign or symptoma | Incidence, *n* (%)*N* = 782 patients |
| Pyrexia | 138 (17.6) |
| Productive cough | 95 (12.1) |
| Dyspnea  | 77 (9.8) |
| Pain | 76 (9.7) |
| Swelling | 65 (8.3) |
| Cough | 62 (7.9) |
| Erythema | 51 (6.5) |
| Abdominal pain | 46 (5.9) |
| Inflammation  | 45 (5.8) |
| Malaise | 40 (5.1) |
| Tenderness | 39 (5.0) |
| Rash | 32 (4.1) |
| Diarrhea  | 28 (3.6) |
| Edema | 26 (3.3) |
| Shock | 23 (2.9) |
| Vomiting | 22 (2.8) |
| Feeling hot | 21 (2.7) |
| Chest pain | 20 (2.6) |
| Hemorrhage | 20 (2.6) |
| Back pain | 17 (2.2) |
| Chills | 16 (2.1) |
| Nausea | 15 (1.9) |
| Decreased appetite  | 15 (1.9) |
| Arthralgia | 12 (1.5) |
| Mass | 11 (1.4) |
| Glycosuria  | 11 (1.4) |
| Depressed level of consciousness | 10 (1.3) |
| Decrease platelet count | 10 (1.3) |
| Blister  | 10 (1.3) |
| Decreased blood pressure  | 8 (1.0) |

aMedDRA preferred term