**Drug Safety**

**Pediatric drug safety signal detection: A new drug-event reference set for performance testing of data-mining methods and systems**

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**Appendix 1: Medline search algorithms for sudden death-** **cyproterone/ethinyl estradiol (negative control) and sudden death-clarithromycin (positive control)**

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| **Association** | **Concept** | **Algorithm** |
| sudden death- cyproterone/ethinyl estradiol | sudden death | (exp Death, Sudden/ OR (((sudden\* OR unexpect\* OR instant\*) adj3 (death OR dead OR died OR dying)) OR mors subita).ab,ti.) |
|  |  | AND |
|  | cyproterone/ ethinylestradiol | (Estradiol/aa and Cyproterone Acetate/) or ((cyproterone acetate adj3 (ethinyl estradiol or ethinyloestradiol)) or co cyprindiol or cocyprindiol or climen or diane or dianette).ab,ti. |
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| sudden death- clarithromycin | sudden death | (exp Death, Sudden/ OR (((sudden\* OR unexpect\* OR instant\*) adj3 (death OR dead OR died OR dying)) OR mors subita).ab,ti.) |
|  |  | AND |
|  | general adverse drug reaction | drug toxicity/ |
|  |  | AND |
|  | clarithromycin | clarithromycin/ |

**Note:** For each association, the search results were limited to articles published in English

**Appendix 2: Medical definitions of selected adverse events; and corresponding proposed but unvalidated Medical Definition for Regulatory Activities (MedDRA) codes (SMQ-standardized MedDRA query; PT-preferred term; LT-lower level term; HT-high level term; HG- high level group term; OL-noncurrent lower level term)**

| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
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| **1** | **bullous eruptions** | **fixed drug eruption**  These are reactions characterized by:   1. One or more sharply demarcated, erythematous lesions, sometimes leading to a blister. 2. Hyperpigmentation which often results after resolution of the acute inflammation. 3. With rechallenge, the lesion recurs in the same (i.e., fixed) location. 4. Lesions often involve the lips, hands, legs, face, genitalia, and oral mucosa and cause a burning sensation. 5. Most patients have multiple lesions.   **See references for further details** | 1. Shinkai K, Roujeau J, Stern RS, Wintroub BU. Chapter 55. Cutaneous Drug Reactions. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=9098524. Accessed October 1, 2012 2. Stern RS, Shear NH. Cutaneous reactions to drugs and biological modifiers. In: Cutaneous Medicine and Surgery, Arndt KA, LeBoit PE, Robinson JK, Wintroub BU (Eds), WB Saunders, Philadelphia 1996. Vol 1, p.412. 3. Yawalkar N. Drug-induced exanthems. Toxicology. 2005;209:131–134. doi: 10.1016/j.tox.2004.12.023 | (LT/10016740), (LT/10048796) |
|  |  | **erythema multiforme**  Characteristics include:   1. Acute self-limited, usually mild and often relapsing muco-cutaneous syndrome. 2. Usually benign but with frequent recurrences 3. The skin lesions are usually target-shaped plaques with or without central blisters, predominant on the face and extremities.   **sub-types**   1. Erythema multiforme minor: Skin lesions without involvement of mucous membranes 2. Erythema multiforme major: Skin lesions with involvement of mucous membranes 3. Mucosal erythema multiforme (Fuchs syndrome, ectodermosis pluriorificialis): Mucous membrane lesions without cutaneous involvement   **See references for further details** | 1. Roujeau J. Chapter 39. Erythema Multiforme. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Dallas NA, eds. *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=56032944. Accessed October 2, 2012. | (LT/10015217), (LT/10015218),(LT/10015221), (LT/10015222), (LT/10015223), (LT/10015223), (LT/10015224), (LT/10033726), (LT/10033730), (LT/10037876), (LT/10040843), (LT/10044259), (LT/10057783), (LT/10057866), (LT/10057970), (LT/10057971), (LT/10068560), (PT/10015218), (PT/10037876), (PT/10057970) |
|  |  | **epidermal necrolysis (Stevens-Johnsons Syndrome and toxic epidermal necrolysis)**  Characteristics include:   1. They are “rare and life-threatening, mainly drug induced”. 2. There is “widespread apoptosis of keratinocytes provoked by the activation of a cell-mediated cytotoxic reaction and amplified by cytokines, mainly granulysin” 3. “Confluent purpuric and erythematous macules evolving to flaccid blisters and epidermal detachment predominating on the trunk and upper limbs and associated with mucous membrane involvement”. 4. Pathologic analysis shows full-thickness necrosis of epidermis associated with mild mononuclear cell infiltrate   **See references for further details** | 1. Valeyrie-Allanore L, Roujeau J. Chapter 40. Epidermal Necrolysis (Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis). In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Dallas NA, eds. *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=56033128. Accessed October 2, 2012. | (LT/10006561), (LT/10015156), (LT/10015209), (LT/10015210), (LT/10015211), (LT/10015219), (LT/10015220), (LT/10015222), (LT/10028077), (LT/10030068), (LT/10030081), (LT/10042029), (LT/10042030), (LT/10042033), (LT/10042849), (LT/10047376), (OL/10042032), (PT/10030081), (PT/10042033), (LT/10014986), (LT/10025166), (LT/10025167), (LT/10025168), (LT/10028848), (LT/10028849), (LT/10043221), (LT/10044223), (OL/10025165), (OL/10042821), (OL/10044222), (PT/10044223) |

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| **2** | **aplastic anemia** | Aplastic anemia is characterized by the suppression of all bone marrow lines – erythroid, granulocytic and megakaryocytic ultimately leading to pancytopenia  **Characteristics**   1. Pancytopenia 2. Hypocellular bone marrow 3. Normal hematopoetic cells   **See references for further details** | * 1. Primack BA, Mahaniah KJ. Chapter 31. Anemia. In: South-Paul JE, Matheny SC, Lewis EL, eds. *CURRENT Diagnosis & Treatment in Family Medicine*. 3rd ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=8153552. Accessed October 2, 2012   2. Neal S. Young; Acquired Aplastic Anemia. Annals of Internal Medicine. 2002 Apr;136(7):534-546   3. Guinan EC. Diagnosis and management of aplastic anemia. Hematology Am Soc Hematol Educ Program. 2011;2011:76–81 | (LT/10049494), (LT/10002037),(LT/10002038), (LT/10002061), (LT/10002274), (LT/10002274), (LT/10002275), (LT/10002294), (LT/10002962), (LT/10002967), (LT/10002968), (LT/10002969), (LT/10002970), (LT/10002971), (LT/10003506), (LT/10004738), (LT/10005980), (LT/10005984), (LT/10005986), (LT/10005987), (LT/10010776), (LT/10010777), (LT/10012381), (LT/10020954), (LT/10021069), (LT/10021074), (LT/10021075), (LT/10021077), (LT/10026846), (LT/10026848), (LT/10026853), (LT/10033661), (LT/10036699), (LT/10048580), (LT/10051779), (LT/10053138), (LT/10053213), (LT/10053504), (LT/10054329), (LT/10054361), (LT/10054580), (LT/10057528), (LT/10064566), (LT/10065553), (LT/10068061), (LT/10068063), (LT/10071576), (LT/10071584), (PT/10002967), (PT/10003506), (PT/10004738), (PT/10021074), (PT/10033661), (PT/10051779), (PT/10053138), (PT/10053213), (PT/10053504), (PT/10057528), (PT/10065553), (PT/10071576) |

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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **3** | **Agranulocytosis** | **agranulocytosis** means the absence of granulocytes (i.e. Absolute Neutrophil count of zero).  However, **“agranulocytosis or acute neutropenia** currently refers to a profound decrease or an absolute lack of circulating granulocytes, classically resulting in a neutrophil count of ***<0.5 × 10^9/l”***  In the majority of patients, the neutrophil count is ***< 0.1 × 10^9/l***  **See references for further details** | 1. Andres E., Zimmer J., Mecili M., Weitten T., Alt M., Maloisel F. Clinical presentation and management of drug-induced agranulocytosis. Expert Rev. Hematol. 2011; 4 (2): 143- 151 2. Frank Andersohn, Christine Konzen, Edeltraut Garbe; Systematic Review: Agranulocytosis Induced by Nonchemotherapy Drugs. Annals of Internal Medicine. 2007 May;146(9):657-665 | (LT/10001507), (LT/10003506), (LT/10004738), (LT/10005984), (LT/10018687), (LT/10029366), (LT/10029369), (LT/10029382), (LT/10050443), (LT/10051645), (LT/10057528), (LT/10066542), (PT/10001507), (PT/10003506),(PT/10004738), (PT/10018687), (PT/10029366),(PT/10050443), (PT/10051645), (PT/10057528), (SMQ/20000023) |
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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **4** | **Thrombocytopenia** | Thrombocytopenia can be defined as follows:   1. **Level 1 of diagnostic certainty (confirmed TP):**   Platelet count less than ***150×109 L−1***  **AND**  confirmed by blood smear examination OR the presence of clinical signs and symptoms of spontaneous bleeding.   1. **Level 2 of diagnostic certainty (unconfirmed TP):** Platelet count less than 150×109 L−1   ***Drug-induced thrombocytopenia (DITP)*** *should be suspected in a patient who presents with new onset of thrombocytopenia without an obvious cause other than drug ingestion. A patient with recurrent episodes of acute thrombocytopenia should be suspected of having a drug-induced etiology. A detailed history, including all of the medications being taken by the patient, is essential. This should include all prescribed drugs, over-the-counter medications, herbal preparations, folk remedies, quinine-containing beverages, and recent vaccinations.*  **See references for further details** | 1. Wise RP*,* Bonhoeffer J*,* Beeler J*, et al.* Thrombocytopenia: Case definition and guidelines for collection, analysis, and presentation of immunization safety data*.* Vaccine2007*;* 25*:* 5717*–*5724 2. Royer, D. J., George, J. N. and Terrell, D. R. (2010), Thrombocytopenia as an adverse effect of complementary and alternative medicines, herbal remedies, nutritional supplements, foods, and beverages. European Journal of Haematology, 84: 421–429 | (HG/10035534), (HT/10035533), (HT/10043555), (LT/10012530), (LT/10024922), (LT/10035524), (LT/10035526), (LT/10035527), (LT/10035528), (LT/10035529), (LT/10035531), (LT/10035532), (LT/10035540), (LT/10035545), (LT/10036735), (LT/10037557), (LT/10037561), (LT/10038213), (LT/10039884), (LT/10043545), (LT/10043546), (LT/10043552), (LT/10043553), (LT/10043554), (LT/10043556), (LT/10043557), (LT/10043558), (LT/10043559), (LT/10043560), (LT/10043561), (LT/10043569), (LT/10044394), (LT/10048672), (LT/10050245), (LT/10051057), (LT/10051601), (LT/10058336), (LT/10062506), (LT/10063129), (LT/10066667), (LT/10070664), (LT/10072326), (LT/10072332), (MTH\_SMQ/20000031), (OL/10013258), (OL/10043551), (PT/10035526), (PT/10035528), (PT/10035531), (PT/10035532), (PT/10035540), (PT/10037557), (PT/10043554), (PT/10043557), (PT/10043561), (PT/10050245), (PT/10062506), (PT/10070664), (PT/10072326), (SMQ/20000031) |

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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **5** | **psychosis** | **‘psychosis** is a disturbance in the perception of reality, evidenced by hallucinations, delusions, or thought disorganization. Psychotic states are periods of high risk for agitation, aggression, impulsivity, and other forms of behavioral dysfunction’  **‘*hallucinations*** are false sensory perceptions occurring in any of the five sensory modalities. Auditory hallucinations are the most common, followed by visual, tactile, olfactory, and gustatory’  **‘*delusions*** are false beliefs that are firmly held despite obvious evidence to the contrary, and not typical of the patient's culture, faith, or family. Persecutory, grandiose, religious, somatic, and other delusions are all common and cut across diagnostic boundaries’  **‘*thought disorganization*** - disruption of the logical process of thought may be represented by loose associations, nonsensical speech, or bizarre behavior. These symptoms are typically accompanied by a high level of functional impairment and high risk for agitated and aggressive behavior’  **See references for further details** | 1. Shelton RC. Chapter 17. Other Psychotic Disorders. In: Ebert MH, Loosen PT, Nurcombe B, Leckman JF, eds. *CURRENT Diagnosis & Treatment: Psychiatry*. 2nd ed. New York: McGraw-Hill; 2008. http://www.accessmedicine.com/content.aspx?aID=3284695. Accessed October 2, 2012. 2. UpToDate. *Overview of psychosis*. 2013 [cited 2014 19th June]; Available from: <http://www.uptodate.com/contents/overview-of-psychosis?source=search_result&search=overview+of+psychosis&selectedTitle=1~150>. | (HT/10004938), (HT/10006360), (HT/10012259), (LT/10000958), (LT/10001022), (LT/10001443), (LT/10001444), (LT/10001445), (LT/10001449), (LT/10001450), (LT/10001451), (LT/10004908), (LT/10004935), (LT/10008522), (LT/10008524), (LT/10009080), (LT/10011717), (LT/10012239), (LT/10012240), (LT/10012241), (LT/10012242), (LT/10012243), (LT/10012244), (LT/10012245), (LT/10012246), (LT/10012247), (LT/10012247), (LT/10012248), (LT/10012257), (LT/10012260), (LT/10012261), (LT/10012262), (LT/10012287), (LT/10012393), (LT/10012408), (LT/10013143), (LT/10013144), (LT/10013145), (LT/10013708), (LT/10013741), (LT/10013758), (LT/10013759), (LT/10013761), (LT/10015134), (LT/10015626), (LT/10016894), (LT/10018669), (LT/10018671), (LT/10019379), (LT/10021031), (LT/10021166), (LT/10021720), (LT/10023164), (LT/10026754), (LT/10026755), (LT/10026756), (LT/10026757), (LT/10026758), (LT/10026780), (LT/10026781), (LT/10026784), (LT/10026785), (LT/10026786), (LT/10026787), (LT/10026789), (LT/10026790), (LT/10026791), (LT/10027740), (LT/10027945), (LT/10033864), (LT/10033867), (LT/10033870), (LT/10034702), (LT/10037200), (LT/10037234), (LT/10037235), (LT/10037237), (LT/10037238), (LT/10037239), (LT/10037240), (LT/10037241), (LT/10037242), (LT/10037243), (LT/10037245), (LT/10037248), (LT/10037250), (LT/10037253), (LT/10037953), (LT/10037954), (LT/10039612), (LT/10039613), (LT/10039621), (LT/10039622), (LT/10039635), (LT/10039987), (LT/10040534), (LT/10040535), (LT/10041317), (LT/10041317), (LT/10044395), (LT/10045620), (LT/10045654), (LT/10045655), (LT/10045656), (LT/10045855), (LT/10045856), (LT/10046122), (LT/10046160), (LT/10048343), (LT/10053415), (LT/10053632), (LT/10056309), (LT/10056326), (LT/10057667), (LT/10059232), (LT/10059419), (LT/10061040), (LT/10061920), (LT/10062645), (LT/10063033), (LT/10065617), (LT/10066731), (LT/10068305), (LT/10070669), (LT/10072389), (LT/10072392), (OL/10001437), (OL/10001448), (OL/10004918), (OL/10013739), (OL/10025459), (OL/10025460), (OL/10026788), (OL/10031481), (OL/10031518), (OL/10031602), (OL/10031619), (OL/10032253), (OL/10032711), (OL/10032712), (OL/10032889), (OL/10033866), (OL/10037221), (PT/10001022), (PT/10001443), (PT/10008522), (PT/10012239), (PT/10012241), (PT/10012244), (PT/10012245), (PT/10015134), (PT/10018671), (PT/10023164), (PT/10033864), (PT/10034702), (PT/10039621), (PT/10039987), (PT/10040535), (PT/10041317), (PT/10041317), (PT/10053632), (PT/10056326), (PT/10057667), (PT/10059232), (PT/10061040), (PT/10061920), (PT/10062645), (PT/10063033), (PT/10065617), (PT/10070669), (SMQ/20000117) |

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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **6** | **suicide** | **Two concepts** will be considered:   1. completed suicide 2. suicide attempt   **completed suicide**  Death caused by self-directed injurious behavior with any intent to die as a result of the behavior.  **suicide attempt**  A non-fatal self-directed potentially injurious behavior with any intent to die as a result of the behavior. A suicide attempt may or may not result in injury.  **See references for further details** | 1. Crosby AE, Ortega L, Melanson C. Self-directed Violence Surveillance: Uniform Definitions and Recommended Data Elements, Version 1.0. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2011 | (LT/10000394), (LT/10003728), (LT/10010144), (LT/10013738), (LT/10033298), (LT/10033927), (LT/10036001), (LT/10042462), (LT/10042463), (LT/10042464), (LT/10042465), (LT/10042466), (LT/10067875), (OL/10057354), (PT/10010144), (PT/10042464), (SMQ/20000035), (SMQ/20000037) |

| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
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| **7** | **ventricular arrhythmia** | **Three concepts** will be considered:   1. Ventricular Tachycardia 2. Ventricular Fibrillation 3. Bradycardia   **ventricular tachycardia**  This can be defined on the basis of heart rate and ECG findings.  **On the basis of heart rate:**   * >180 beats/minute (regular) in infants and young children * > 120 beats/minute (regular) in older children/adolescents (indicate tachycardia generally)   **On the basis of ECG, the following features apply:**   * Ventricular rate is >120 beats per minute and regular * P waves are often not identifiable, may have AV dissociation, or may have retrograde depolarization * QRS is typically wide (>0.09 sec) * T waves are often opposite in polarity from the QRS complex   **ventricular fibrillation (VF)**  It is characterized by rapid***, chaotic, and asynchronous contraction of the left ventricle.*** The surface electrogram of VF reveals a ***rapid, irregular, dysmorphic pattern with no clearly defined QRS complex.***  **bradycardia**  Normally, the value for average heart rates varies with age. Younger patients usually have higher heart rates which decrease to adult values by the late teenage years.  Bradycardia can be established by either using 12-lead electrocardiogram (ECG) or by 24-hour ambulatory monitoring.  **On the basis of** **12-lead electrocardiogram (ECG):**   * **Newborn to 3 years**: < 100 beats/minute * **3 - 9 years:** < 60 beats/ minute * **9 – 16 years**: < 50 beats per minute   **On the basis of 24-hour ambulatory monitoring:**   * **Newborns – 2 years:** < 60 beats/minute while asleep and < 80 beats/ minute while awake * **2 – 6 years:** < 60 beats per minute * **6 – 11 years:** < 45 beats/ minute * **> 11 years (adolescents):** < 40 beats/minute * **> 11 years who are well-trained athletes:** < 30 beats per minute   **N.B** The 24-hour ambulatory guidelines vary from the ECG guidelines as they include the slower heart rates that occur normally at rest and sleep  **See references for further details** | 1. UpToDate. *Causes of wide QRS complex tachycardia in children*. 2014 [cited 2014 19th June]; Available from: <http://www.uptodate.com/contents/causes-of-wide-qrs-complex-tachycardia-in-children?source=machineLearning&search=causes+of+wide+qrs+tachycardia+in+children&selectedTitle=1~150&sectionRank=1&anchor=H3#H3>. 2. Rho RW, Page RL. Chapter 42. Ventricular Arrhythmias. In: Fuster V, Walsh RA, Harrington RA, eds. *Hurst's The Heart*. 13th ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=7814365. Accessed October 4, 2012 3. Michaelson M, Engle MA. Congenital complete heart block: An international study of the natural history. In: Cardiovascular Clinics, Brest AN, Engle MA (Eds), FA Davis, Philadelphia 1972. p.85 4. Kugler JD. Sinus node dysfunction. In: Pediatric Arrhythmias: Electrophysiology and Pacing, Gillette PC, Garson AG Jr (Eds), WB Saunders, Philadelphia 1990. p.250. | (LT/10003131), (LT/10003132), (LT/10016571), (LT/10016573), (LT/10034048), (LT/10034049), (LT/10034050), (LT/10043082), (LT/10047281), (LT/10047282), (LT/10047290), (LT/10047292), (LT/10047293), (LT/10049447), (LT/10051363), (LT/10060730), (LT/10066663), (LT/10066685), (LT/10066686), (LT/10073034), (OL/10047395), (PT/10047281), (PT/10047290), (PT/10049447) |

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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **8** | **sudden death** | **Two concepts** will be considered:   1. Sudden death 2. Sudden cardiac death   **Sudden death**  **Two definitions** will be considered for sudden death:   1. Unwitnessed death occurring within 24hrs of being seen alive and functioning normally. 2. Natural, unexpected death within 1 hour of the onset of symptoms. Four temporal elements have to be considered in the use of this definition: prodromes, onset of the terminal event, cardiac arrest, and biological death. The 1-hour definition refers to the period between onset of the terminal event, that is, acute changes in cardiovascular status, and cardiac arrest. The biological legal death can occur days or weeks after the cardiac arrest, as patients can survive with irreversible brain damage and life support   **Sudden cardiac death (SCD)**  **Sudden cardiac death (SCD)** is said to have occurred when there is sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation, thereby leading to death (**if corrective measures are not taken rapidly)**  Cardiac arrest should be used to signify an event as described above, that is reversed, usually by CPR and/or defibrillation or cardioversion, or cardiac pacing.  ***Sudden cardiac death should not be used to describe events that are not fatal."***  **See references for further details** | 1. C. van der Werf, I. van Langen, A.A. Wilde. Sudden death in the young: what do we know about it and how to prevent? Circ Arrhythm Electrophysiol, 3 (2010), pp. 96–104 2. UpToDate. *Overview of sudden cardiac arrest and sudden cardiac death*. 2013 [cited 2014 19th June]; Available from: <http://www.uptodate.com/contents/overview-of-sudden-cardiac-arrest-and-sudden-cardiac-death?source=search_result&search=overview+of+sudden+cardiac+arrest+and+sudden+cardiac+death&selectedTitle=1~150>. | (HT/10011907), (LT/10042434), (LT/10042435), (LT/10042436), (LT/10042437), (LT/10046269), (LT/10049418), (LT/10052810), (LT/10063894), (LT/10063895), (LT/10069409), (OL/10011915), (OL/10011938), (PT/10042434), (PT/10049418), (PT/10063894) |

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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **9** | **QT prolongation** | **Torsades de pointes (TdP)** will be included in this definition  **QT prolongation**  It refers to prolongation of heart rate-corrected QT (QTc) interval from a 12-lead electrocardiogram (ECG).  For ***children aged 1 – 15 years***, prolonged QTc is defined as:   * **> 460 milliseconds**   Bazett formula (QTc=QT/RR0.5) is most often used for heart rate correction  **Long QT syndrome (LQTS)**  This is characterized by prolonged QT with clinical manifestations/sequelae like palpitations, syncope, seizures, and sudden cardiac death (SCD).  **Torsades de pointes (TdP)**  Torsades de pointes (TdP) is a form of polymorphic ventricular tachycardia (VT) that occurs in the setting of acquired or congenital QT interval prolongation. It is usually found on ECG.  **Polymorphic VT** is defined as a ventricular rhythm faster than 100 beats per min with frequent variations of the QRS axis, morphology, or both. ***In the specific case of TdP, these variations take the form of a progressive, sinusoidal, cyclic alteration of the QRS axis.*** ***The peaks of the QRS complexes appear to "twist" around the isoelectric line of the recording; hence the name torsades de pointes or "twisting of the points."***  **See references for further details** | 1. ICH Topic E 14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non Antiarrhythmic Drugs; CPMP/986/96. The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. London: Committee for proprietary medicinal products. 1997 2. UpToDate. *Definition of normal, borderline, and prolonged corrected QT interval (QTc) in seconds according to age and gender*. [cited 2012 18th October]; Available from: <http://www.uptodate.com/contents/image?imageKey=CARD/78934&topicKey=CARD%2F1053&source=preview&rank=undefined>. 3. El-Sherif N, Turitto G. Torsade de pointes. Curr Opin Cardiol 2003;18(1):6–13 4. Passman R, Kadish A. Polymorphic ventricular tachycardia, long Q-T syndrome, and torsades de pointes. *Med Clin North Am*. 2001;85: 321–341. | (LT/10014383), (LT/10014387), (LT/10024802), (LT/10024803), (LT/10036887), (LT/10037094), (LT/10037700), (LT/10037703), (LT/10037705), (LT/10044066), (LT/10044067), (LT/10053604), (LT/10053698), (LT/10054581), (PT/10014387), (PT/10024803), (PT/10044066), (SMQ/20000001) |

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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **10** | **venous thromboembolism** | **Two manifestations** of venous thromboembolism will be considered:   1. Deep venous thrombosis (DVT) 2. Pulmonary thromboembolism (PE)   **deep venous thrombosis (DVT)**  This is characterized by:   * Leg pain * Inguinal or abdominal pain * Swelling, and reddish or purple discoloration of the legs * Palpable cord (reflecting a thrombosed vein), * Ipsilateral edema * Warmth, and/or superficial venous dilation * “Positive” result on **compression** **ultrasonography** * “Positive” result on **impedance plethysmography** * “Positive” result on **contrast venography** (**reference test**).   **pulmonary thromboembolism (PE)**  This is characterized by:   * Pleuritic chest pain * Tachypnea * Cough * Tachycardia * Acute dyspnea * Sudden collapse * Leukocytosis * Increased erythrocyte sedimentation rate (ESR) * Elevated serum LDH or AST (SGOT) with a normal serum bilirubin * **Arterial blood gases**: hypoxemia, hypocapnia, and respiratory alkalosis   **See references for further details** | 1. UpToDate. *Pathogenesis and clinical manifestations of venous thrombosis and thromboembolism in infants and children*. 2013 [cited 2014 19th June]; Available from: <http://www.uptodate.com/contents/pathogenesis-and-clinical-manifestations-of-venous-thrombosis-and-thromboembolism-in-infants-and-children?source=search_result&search=pathogenesis+and+clinical+manifestation+of+thrombosis+and+thromboembolism+in+children&selectedTitle=1~150>. 2. Lensing AWA, Prandoni P, Prins HR, Büller HR. Deep-vein thrombosis. Lancet. 1999;353:479-485. 3. Hirsh J, Hull RD, Raskob GE. Clinical features and diagnosis of venous thrombosis. J Am Coll Cardiol 1986;8:114B-27B 4. Wells PS, Hirsh J, Anderson DR, et al.  Accuracy of clinical assessment of deep-vein thrombosis . Lancet . 1995;;345:1326-1330. 5. Kahn SR, Joseph L, Abenhaim L, Leclerc JR. Clinical prediction of deep vein thrombosis in patients with leg symptoms. Thromb Haemost. 1999;81:353-7 6. Donnelly R, Emslie-Smith AM, Gardner ID, Morris AD. ABC of arterial and venous disease. Non-invasive methods of arterial and venous assessment. Br Med J 2000;320:698–701. 7. Hull R, Taylor DW, Hirsh J, Sackett DL, Powers P, Turpie AGG, Walker ID: Impedance plethysmography: The relationship between venous filling and sensitivity and specificity for proximal vein thrombosis. Circulation 58:898, 1978 8. Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, Powers P, Gent M: Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation. 1981; 64(3):622. 9. Lensing AW, Büller HR, Prandoni P, Batchelor D, Molenaar AH, Cogo A, Vigo M, Huisman PM, ten Cate JW. Contrast venography, the gold standard for the diagnosis of deep-vein thrombosis: improvement in observer agreement. Thromb Haemost. 1992;67(1):8.   (10) Buck JR, Connors RH, Coon WW, Weintraub WH, Wesley JR, Coran AG. Pulmonary embolism in children. J Pediatr Surg. 1981;16(3):385.  (11) Byard RW, Cutz E. Sudden and unexpected death in infancy and childhood due to pulmonary thromboembolism. An autopsy study. Arch Pathol Lab Med. 1990;114(2):142.  (12)Matthew DJ, Levin M. Pulmonary thromboembolism in children. Intensive Care Med. 1986;12(6):404. | (HT/10037379), (HT/10037379), (HT/10047197), (LT/10000853), (LT/10012098), (LT/10012107), (LT/10013877), (LT/10013879), (LT/10014521), (LT/10014537), (LT/10034272), (LT/10037377), (LT/10037380), (LT/10037436), (LT/10038547), (LT/10043566), (LT/10043567), (LT/10043578), (LT/10043630), (LT/10043642), (LT/10047251), (LT/10047252), (LT/10049915), (LT/10049916), (LT/10049917), (LT/10049918), (LT/10050071), (LT/10051055), (LT/10054751), (LT/10056966), (LT/10064602), (LT/10065052), (LT/10066529), (LT/10066738), (LT/10066899), (LT/10073531), (OL/10014511), (OL/10034191), (OL/10037378), (PT/10034272), (PT/10037377), (PT/10038547), (PT/10051055), (PT/10064602) |

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| **S/N** | **Event** | **Case definition** | **References** | **MedDRA codes** |
| **11** | **anaphylaxis** | See Brighton Collaboration case definition | 1. [Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data.](http://www.ncbi.nlm.nih.gov/pubmed/17448577) 2. Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, de Souza Brito G, Heininger U, Imoukhuede B, Khamesipour A, Erlewyn-Lajeunesse M, Martin S, Mäkelä M, Nell P, Pool V, Simpson N; Brighton Collaboration Anaphylaxis Working Group. 3. Vaccine. 2007 Aug 1;25(31):5675-84. Epub 2007 Mar 12. | (SMQ/20000071) |

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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **12** | **seizure** | This is defined in 3 levels with respect to diagnostic certainty. All levels are acceptable.  **Level 1 of diagnostic certainty**   1. witnessed sudden loss of consciousness ***AND*** 2. generalized, tonic, clonic, tonic–clonic, or or atonic motor manifestations.   **Level 2 of diagnostic certainty**  history of unconsciousness ***AND***   1. generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.   **Level 3 of diagnostic certainty**   1. history of unconsciousness ***AND*** 2. other generalized motor manifestations   **See references for further details** | 1. Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher M, et al. (2004) Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 22 (5–6): 557–562 | (SMQ/20000212) |

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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **13** | **acute kidney injury (AKI)** | **‘acute kidney injury (AKI)** is defined as a decrease in glomerular filtration rate (GFR), which traditionally is manifested by an elevated or a rise in serum creatinine. However, serum creatinine is often a delayed and imprecise test as it reflects GFR in individuals at steady state with stable kidney function, and does not accurately estimate the GFR in a patient whose renal function is changing’  ‘The term AKI has largely replaced acute renal failure (ARF) as it more clearly defines renal dysfunction as a continuum rather than a discrete finding of failed kidney function’  **pediatric AKI** presents as a wide range of clinical manifestations from a minimal elevation in serum creatinine to anuric renal failure, arises from multiple causes, and occurs in a variety of clinical settings. Below are the normal range of values of serum creatinine for different pediatric age groups:   * **Newborn** – 0.3 to 1.0 mg/dL (27 to 88 micromol/L) * **Infant** – 0.2 to 0.4 mg/dL (18 to 35 micromol/L) * **Child** – 0.3 to 0.7 mg/dL (27 to 62 micromol/L) * **Adolescent** – 0.5 to 1.0 mg/dL (44 to 88 micromol/L)   **See references for further details** | 1. Nephrology TA. The American Society of Nephrology Renal Research Report. J Am Soc Nephrol. 2005;16:1886–1903 2. Devarajan P. Update on mechanisms of ischemic acute kidney injury. J Am Soc Nephrol 2006; 17: 1503–1520 3. Devarajan P. Emerging urinary biomarkers in the diagnosis of acute kidney injury. Expert Opin Med Diagn. 2008;2:387–398 4. Zappitelli M. Epidemiology and diagnosis of acute kidney injury. *Semin Nephrol* 28: 436–446, 2008 5. Andreoli SP: Acute kidney injury in children. *Pediatr Nephrol* 2009; 24:253–263 6. Askenazi D. Evaluation and Management of Critically Ill Children with Acute Kidney Injury. Curr Opin Pediatr. 2011 April ; 23(2): 201–207. doi:10.1097/MOP.0b013e328342ff37. 7. Devarajan P (2011) Biomarkers for the early detection of acute kidney injury. Curr Opin Pediatr 23: 194–200. 10.1097/MOP.0b013e328343f4dd [doi] 8. The Harriet Lane Handbook, 19th ed, Tschudy KM, Arcara KM (Eds), Mosby, St. Louis 2012. p.642. | (HT/10038443), (LT/10000821), (LT/10000952), (LT/10001041), (LT/10001049), (LT/10001051), (LT/10001099), (LT/10005481), (LT/10005483), (LT/10009254), (LT/10009255), (LT/10011361), (LT/10011363), (LT/10011372), (LT/10011373), (LT/10011375), (LT/10016150), (LT/10021678), (LT/10022436), (LT/10022865), (LT/10022870), (LT/10022872), (LT/10023414), (LT/10023419), (LT/10024963), (LT/10028864), (LT/10028865), (LT/10028876), (LT/10029162), (LT/10033695), (LT/10033699), (LT/10033711), (LT/10035276), (LT/10035278), (LT/10037825), (LT/10038422), (LT/10038436), (LT/10038437), (LT/10038438), (LT/10038439), (LT/10038440), (LT/10038441), (LT/10038479), (LT/10038491), (LT/10038493), (LT/10038494), (LT/10038526), (LT/10038541), (LT/10040233), (LT/10055003), (LT/10056221), (LT/10061436), (LT/10068447), (LT/10068736), (LT/10069339), (OL/10001047), (OL/10001048), (OL/10001048), (OL/10001050), (PT/10005481), (PT/10005483), (PT/10011372), (PT/10022870), (PT/10038422), (PT/10038436), (PT/10038491), (PT/10055003), (PT/10068447), (SMQ/20000003) |
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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
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| **14** | **acute liver injury (ALI)** | Only potential cases of drug-induced liver injury (DILI) are of interest; an important requirement will be the availability or otherwise of histological data. The following manifestations will be considered:   * Hepatic necrosis * Liver cirrhosis * Other cases of DILI in which there is no histological data available  1. **On the basis of *availability of histological data:*** 2. **hepatic necrosis:** characterized by  * Death of hepatic parenchyma: single cell (necrobiosis), or multicell in piecemeal, focal, periacinar, midzonal, periportal or paracentral locations. * Massive necrosis: refers to events in individual acini in which all hepatocytes are dead.  1. **liver cirrhosis:** Features include  * Necrosis of liver cells, slowly progressive over a long period and ultimately causing chronic liver failure and death * Fibrosis, involving both central veins and portal areas * Regenerative nodules, the result of hyperplasia of surviving liver cells * Distortion of normal hepatic lobular architecture * Diffuse involvement of the whole liver   **Note:**  A regenerative nodule is an abnormal mass of liver cells without a normal cord pattern or central venule and surrounded completely by fibrosis   1. **In the *absence of histological data,* only liver tests (NOT liver function tests) can be used in diagnosis as follows:** 2. **liver injury:**  * Increase of over 2N (2 times N; where N is the upper limit of normal range) in Alanine Aminotransferase (ALT) or Conjugated Bilirubin (CB)   **OR**   * A combined increase in Aspartate Aminotransferase (AST), Alkaline Phosphatase (AP) and Total Bilirubin (TB), provided one ofthem is above 2N   **Various forms of drug-induced liver injury**   * **hepatocellular:** increase of over 2N in ALT alone, or R≥5 [where R (ratio) is the serum acti**v**ity of ALT/serum activit**y** of AP. Each activity is measured as a multiple of N. Both should have been measured together at the time of recognition of liver injury]. * **cholestatic:** Liver injury is designated cholestatic when there is increase of over 2N in AP alone, or R≤2 * **mixed:** occurs when there is a combination of the following: increase in ALT (over 2N) and AP as well as 2<R<5. R ismost useful in patients with jaundice and may vary during the course of liver injury. | 1. Bénichou C.1990 *Criteria of drug-induced liver disorders. Report of an international consensus meeting.* J Hepatol*.* 11*:*272*–276* 2. UpToDate. *Drug-induced liver injury*. 2014 [cited 2014 19th June]; Available from: <http://www.uptodate.com/contents/drug-induced-liver-injury?source=search_result&search=drugs+and+the+liver+patterns+of+druinduced+liver+injury&selectedTitle=6~150>. 3. Chandrasoma P., Taylor C.R. (1998). Chapter 43. The Liver: II. Toxic & Metabolic Diseases; Neoplasms. In P. Chandrasoma, C.R. Taylor (Eds), *Concise Pathology*, 3e. Retrieved September 18, 2012 from http://www.accessmedicine.com/content.aspx?aID=189816. | (HT/10019669), (HT/10019833), (LT/10001544), (LT/10001547), (LT/10001548), (LT/10001550), (LT/10001551), (LT/10001669), (LT/10001675), (LT/10001677), (LT/10001679), (LT/10001771), (LT/10001845), (LT/10004659), (LT/10004660), (LT/10004685), (LT/10004697), (LT/10005308), (LT/10005313), (LT/10008639), (LT/10008641), (LT/10009210), (LT/10009211), (LT/10009213), (LT/10009214), (LT/10010689), (LT/10010690), (LT/10011853), (LT/10013705), (LT/10013762), (LT/10018455), (LT/10018457), (LT/10018644), (LT/10019641), (LT/10019642), (LT/10019648), (LT/10019649), (LT/10019684), (LT/10019684), (LT/10019692), (LT/10019693), (LT/10019693), (LT/10019710), (LT/10019754), (LT/10019766) , (LT/10019796), (LT/10019831), (LT/10019832), (LT/10019834), (LT/10019835), (LT/10019837), (LT/10022224), (LT/10022227), (LT/10024665), (LT/10024666), (LT/10024667), (LT/10024668), (LT/10024701), (LT/10028859), (LT/10028867), (LT/10034513), (LT/10034927), (LT/10040133), (LT/10040275), (LT/10040526), (LT/10044345), (LT/10045974), (LT/10049199), (LT/10049228), (LT/10050279), (LT/10056502), (LT/10056806), (LT/10058473), (LT/10059570), (LT/10059571), (LT/10066503), (LT/10066756), (LT/10066756), (LT/10066758), (LT/10067125), (LT/10067718), (LT/10067969), (LT/10067969), (LT/10067970), (LT/10067971), (LT/10070815), (LT/10071561), (LT/10072032), (LT/10072268), (LT/10072734), (LT/10072937), (OL/10000670), (OL/10001673), (OL/10001678),(OL/10003695), (OL/10004708), (OL/10009209),(OL/10018456), (OL/10018643), (OL/10032161),(OL/10039482), (OL/10040274), (PT/10001547),(PT/10001551), (PT/10004659), (PT/10004685), (PT/10019641), (PT/10019692), (PT/10019754), (PT/10019834), (PT/10019837), (PT/10059570), (PT/10059571), (PT/10066758), (PT/10067125), (PT/10067718), (PT/10067969), (PT/10067969), (PT/10070815), (PT/10072268), (SMQ/20000013) |
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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **15** | **sepsis** | **‘Sepsis** refers to Systemic Inflammatory Response Syndrome (SIRS) in the presence of or as a result of suspected or proven infection’  **‘Systemic Inflammatory Response Syndrome (SIRS)** is a widespread inflammatory response that may or may not be associated with infection. ***The presence of two or more of the following criteria (one of which must be abnormal temperature or leukocyte count)*** defines SIRS’:   * Core temperature (measured by rectal, bladder, oral, or central probe) of >38.5ºC or <36ºC * Tachycardia, defined as a mean heart rate >2 standard deviations above normal for age, or for children <1 year of age, bradycardia defined as a mean heart rate <10th percentile for age * Mean respiratory rate >2 standard deviations above normal for age * Leukocyte count elevated or depressed for age, or >10 percent immature neutrophils   **See references for further details** | 1. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005:2–8 | (HT/10040054), (LT/10002714), (LT/10002715), (LT/10011213), (LT/10014824), (LT/10015296), (LT/10027268), (LT/10027280), (LT/10027281), (LT/10028912), (LT/10034110), (LT/10034111), (LT/10034511), (LT/10034690), (LT/10035650), (LT/10035651), (LT/10039444), (LT/10039445), (LT/10040047), (LT/10040048), (LT/10040049), (LT/10040050), (LT/10040051), (LT/10040053), (LT/10040070), (LT/10040070), (LT/10040072), (LT/10040073), (LT/10040078), (LT/10040079), (LT/10040081), (LT/10040082), (LT/10040083), (LT/10040084), (LT/10040085), (LT/10040086), (LT/10040087), (LT/10040088), (LT/10040089), (LT/10040092), (LT/10040095), (LT/10040096), (LT/10040097), (LT/10040580), (LT/10040580), (LT/10041930), (LT/10041931), (LT/10042184), (LT/10042185), (LT/10042197), (LT/10045470), (LT/10045471), (LT/10046161), (LT/10046231), (LT/10046237), (LT/10047431), (LT/10047434), (LT/10048960), (LT/10049151), (LT/10049253), (LT/10049665), (LT/10051017), (LT/10051018), (LT/10051080), (LT/10051379), (LT/10051379), (LT/10051739), (LT/10053022), (LT/10053166), (LT/10053588), (LT/10053596), (LT/10053597), (LT/10053598), (LT/10053599), (LT/10053600), (LT/10053840), (LT/10053879), (LT/10053879), (LT/10054047), (LT/10054137), (LT/10054160), (LT/10054162), (LT/10054167), (LT/10054168), (LT/10054169), (LT/10054170), (LT/10054177), (LT/10054188), (LT/10054189), (LT/10054210), (LT/10054213), (LT/10054219), (LT/10054221), (LT/10054249), (LT/10054250), (LT/10054252), (LT/10054253), (LT/10054254), (LT/10054255), (LT/10054256), (LT/10054257), (LT/10054264), (LT/10054284), (LT/10054608), (LT/10054611), (LT/10054612), (LT/10054613), (LT/10054615), (LT/10054616), (LT/10054617), (LT/10054618), (LT/10054619), (LT/10054620), (LT/10054637), (LT/10054641), (LT/10054642), (LT/10054688), (LT/10054691), (LT/10055078), (LT/10056430), (LT/10057767), (LT/10057847), (LT/10058040), (LT/10058041), (LT/10058867), (LT/10058872), (LT/10058873), (LT/10058874), (LT/10058875), (LT/10058876), (LT/10058877), (LT/10058878), (LT/10058879), (LT/10058888), (LT/10058889), (LT/10058973), (LT/10059070), (LT/10060410), (LT/10060411), (LT/10060413), (LT/10060437), (LT/10062357), (LT/10062357), (LT/10063085), (LT/10064952), (LT/10066745), (LT/10069141), (LT/10069141), (LT/10069684), (LT/10070681), (LT/10071362),(MTH\_HT/10040054), (MTH\_LT/10040078), (MTH\_LT/10040082), (MTH\_LT/10047431), (OL/10021867), (OL/10021901), (PT/10014824), (PT/10015296), (PT/10027280), (PT/10040047), (PT/10040049), (PT/10040051), (PT/10040070), (PT/10040070), (PT/10045470), (PT/10048960), (PT/10049151), (PT/10051017), (PT/10051018), (PT/10051379), (PT/10051379), (PT/10051739), (PT/10053166), (PT/10053588), (PT/10053840), (PT/10053879), (PT/10053879), (PT/10054047), (PT/10054137), (PT/10054160), (PT/10054162), (PT/10054177), (PT/10054210), (PT/10054213), (PT/10054219), (PT/10054221), (PT/10054264), (PT/10056430), (PT/10057767), (PT/10057847), (PT/10058040), (PT/10058041), (PT/10058872), (PT/10058873), (PT/10058874), (PT/10058875), (PT/10058876), (PT/10058877), (PT/10058878), (PT/10058879), (PT/10058889), (PT/10058973), (PT/10059070), (PT/10063085), (PT/10064952), (PT/10069141), (PT/10069141), (PT/10069684), (PT/10070681), (PT/10071362), (SMQ/20000070) |

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| **S/N** | **Event** | **Medical (case) definition** | **References** | **MedDRA codes** |
| **16** | **sudden infant death syndrome (SIDS)** | **‘sudden infant death syndrome (SIDS)** is defined as the sudden death of an infant younger than one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history’.  ‘This definition emphasizes the necessity of autopsy, death scene investigation, and review of the clinical history when making the diagnosis of SIDS, to exclude other explanations for the sudden unexpected infant death that can mimic SIDS’.  **See references for further details** | 1. CDC(1996) Sudden infant death syndrome—United States, 1983–94. MMWR Morb Mortal Wkly Rep 45:859–863 2. Willinger M, James LS, Catz C. Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development. Pediatr Pathol.1991;11 :677– 684 | (LT/10011220), (LT/10011910), (LT/10040666),(LT/10040667), (LT/10042439), (LT/10042440), (LT/10055089), (LT/10055090), (LT/10055091), (LT/10055092), (LT/10069606), (OL/10011939), (OL/10021733), (PT/10042440) |

**Appendix 3:** Evaluation of all positive drug-event associations.

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| ATC Code | Drug Name | Adverse Event (AE) Type | Labelled as AE in SPC [Yes/No] | Type/No. of Supporting Literature Citations |
| J01FA09 | clarithromycin | bullous eruption | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 7  Cohort study = 2  Case report = 5 |
| J01CF05 | doxycycline | bullous eruption | Yes  #eMC (Undesirable effects)  Micromedex (Summary): Adverse effects→serious | Total number of supporting citations = 5  Case report = 3  Case series = 2 |
| J04AC01 | isoniazid | bullous eruption | Yes  #eMC (Undesirable effects)  Micromedex (Drugdex): Cautions → Adverse Reactions | Total number of supporting citations = 6  Clinical Trial = 1  Cohort study = 1  Case report = 4 |
| P01BC01 | quinine | bullous eruption | Yes  Dailymed (Adverse reactions)  Micromedex (Summary): Contraindications/Warnings→ precautions | Total number of supporting citations = 2  Case report = 1  Case series = 1 |
| M01AE01 | ibuprofen | bullous eruption | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 10  Case report = 5  Case series = 5 |
| P01BC01 | quinine | aplastic anaemia | Yes  #eMC (Undesirable effects)  Micromedex (Drugdex): Cautions → Adverse Reactions | Total number of supporting citations = 4  Biological study = 1  Case report = 3 |
| P02CA01 | mebendazole | agranulocytosis | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Drugdex): Cautions → Adverse Reactions | Total number of supporting citations = 1  Cohort study = 1 |
| P01BC01 | quinine | agranulocytosis | Yes  #eMC ( Undesirable effects)  Micromedex (Summary): Adverse effects→serious | Total number of supporting citations = 4  Review of biological mechanism = 2  Case report = 2  Note: this was considered a ‘positive control – grade 1’ despite the fact that they were only 2 case reports, because of the availability of biological evidence. |
| J01FA09 | clarithromycin | thrombocytopenia | Yes  #eMC (Undesirable effects)  Micromedex (Drugdex): Cautions → Adverse Reactions | Total number of supporting citations = 1  Case control= 1 |
| J01CF05 | doxycycline | thrombocytopenia | Yes  #eMC (Undesirable effects)  Micromedex (Drugdex): Cautions → Adverse Reactions | Total number of supporting citations = 1  Systematic literature review = 1 |
| P01BC01 | quinine | thrombocytopenia | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ contraindications); (Adverse effects→serious) | Total number of supporting citations = 20  Biological studies = 8  Review of biological studies = 4  Systematic literature review = 1  Review of spontaneous reports = 2  Case report = 4  Case series = 1 |
| M01AE01 | ibuprofen | thrombocytopenia | Yes  #eMC (Undesirable effects)  Micromedex (Summary): Adverse effects→serious | Total number of supporting citations = 3  Clinical trial = 1  Case control =1  Case series = 1 |
| J01FA09 | clarithromycin | psychosis | Yes  #eMC (Undesirable effects)  Micromedex (Drugdex): Cautions → Adverse Reactions | Total number of supporting citations = 4  Case report = 4 |
| J04AC01 | isoniazid | psychosis | Yes  #eMC (Special warnings and precautions for use)  Micromedex (Drugdex): Cautions → Adverse Reactions | Total number of supporting citations = 4  Cohort study = 2  Case report = 2 |
| R03DC03 | montelukast | psychosis | Yes  #eMC (Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 1  Case series = 1 |
| D10BA01 | isotretinoin | psychosis | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 2  Systematic literature review = 1  Case report = 1 |
| N06BA04 | methylphenidate | psychosis | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 4  Biological study = 2  Cross over clinical trial = 1  Case series = 1 |
| D10BA01 | isotretinoin | suicide | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 3  Systematic literature review = 1  Review of spontaneous reports = 1  Review of spontaneous reports and case series = 1 |
| R03DC03 | montelukast | suicide | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 1  Review of spontaneous reports = 1 |
| J01FA09 | clarithromycin | ventricular arrhythmia | Yes  #eMC (Undesirable effects)  Micromedex (Summary): Contraindications/Warnings→ Contraindications; precautions | Total number of supporting citations = 1  Review of spontaneous reports = 1 |
| P01BC01 | quinine | ventricular arrhythmia | Yes  Dailymed (Contraindications; Warnings and Precautions; Adverse reactions)  Micromedex (Summary): (Contraindications/Warnings→ contraindications; precautions); (Adverse effects→serious) | Total number of supporting citations = 1  Case series = 1 |
| A03FA03 | domperidone | ventricular arrhythmia | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 3  Biological study = 1  Cohort study = 1  Case control = 1 |
| J01FA09 | clarithromycin | sudden death | Yes  #eMC (Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 4  Clinical trial = 1  Case-control = 2  Case report = 1 |
| A03FA03 | domperidone | sudden death | Yes  #eMC (Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 7  Experimental study = 1  Nested case control = 1  Case control = 5 |
| J01FA09 | clarithromycin | QT prolongation | Yes  #eMC (Contraindications; Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ contraindications); (Adverse effects→serious) | Total number of supporting citations = 2  Basic science = 1  Review of spontaneous reports = 1 |
| P01BC01 | quinine | QT prolongation | Yes  #eMC (Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ contraindications; precautions); (Adverse effects→serious) | Total number of supporting citations = 7  Clinical trial = 1  Systematic literature review = 4  Review of spontaneous reports = 1  Case report = 1 |
| M01AE01 | ibuprofen | anaphylaxis | Yes  #eMC (Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious) | Total number of supporting citations = 5  Review of pharmacology = 1  Review of spontaneous reports = 1  Case report = 2  Case series = 1 |
| J04AC01 | isoniazid | seizure | Yes  #eMC (Special warnings and precautions for use)  Micromedex (Summary): Adverse effects→serious | Total number of supporting citations = 8  Review of biological mechanism = 1  Clinical trial = 1  Case report = 5  Case series = 1 |
| P01BC01 | quinine | acute kidney injury | Yes  #eMC (Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious) | Total number of supporting citations = 5  Case report with systematic literature review = 1  Case report = 4 |
| M01AE01 | ibuprofen | acute kidney injury | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious) | Total number of supporting citations = 10  Review of clinical trials = 1  Case control = 1  Case report = 5  Case series = 2  Review of spontaneous reports = 1 |
| J01CF05 | flucloxacillin | acute liver injury | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Drugdex): Cautions → Adverse Reactions | Total number of supporting citations = 11  Cohort study = 2  Literature review = 4  Review of spontaneous reports = 1  Case reports = 3  Case series = 1 |
| J01FA09 | clarithromycin | acute liver injury | Yes  #eMC (Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→ contraindications; precautions); (Adverse effects→serious) | Total number of supporting citations = 3  Cohort study = 1  Case report = 1  Review of spontaneous reports = 1 |
| J05AE06 | lopinavir | acute liver injury | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious) | Total number of supporting citations = 4  Clinical trial = 2  Cohort study = 1  Case report = 1 |
| J04AC01 | isoniazid | acute liver injury | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious) | Total number of supporting citations = 7  Clinical trial = 1  Case report = 4  Case series = 2 |
| P02CA01 | mebendazole | acute liver injury | Yes  Dailymed (Warnings and precautions; Adverse Reactions)  Micromedex (Summary): Adverse effects→serious | Total number of supporting citations = 2  Clinical trial = 1  Case report = 1 |
| P01BC01 | quinine | acute liver injury | Yes  Dailymed (Adverse Reactions)  Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious) | Total number of supporting citations = 3  Case reports = 3 |
| M01AE01 | ibuprofen | acute liver injury | Yes  #eMC (Special warnings and precautions for use; Undesirable effects)  Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious) | Total number of supporting citations = 5  Review of spontaneous reports = 1  Case report = 3  Case series = 1 |

#Electronic Medicines Compendium

**Appendix 4: Comparison of GRiP, EU-ADR [19] and OMOP [20] reference sets: green-positive control, red-negative control.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **PROJECT** | **bullous eruption** | **aplastic anemia** | **agranulo**  **cytosis** | **thrombocyto-penia** | **psy-chosis** | **suicide** | **ventri-cular**  **arrhyth-mia** | **sudden**  **death** | **QT prolongation** | **thrombo**  **embo-lism** | **anaphy-**  **laxis** | **seizure** | **AKI** | **ALI** | **sep**  **sis** | **SIDS** |
| **isoniazid** | GRiP |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| EU-ADR |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| OMOP |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **m’dazole** | GRiP |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| EU-ADR |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| OMOP |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **fluticason** | GRiP |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| EU-ADR |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| OMOP |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **ibuprofen** | GRiP |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| EU-ADR |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| OMOP |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

**Abbreviations: m’dazole – mebendazole; AKI – acute kidney injury; ALI – acute liver injury; SIDS – sudden infant death syndrome**