

Table S1

ROR for hepatic injury of individual drugs ranked according to the strength of the crude association in the population <18 years old

Drug	Number of cases	Number of non-cases	ROR (95% CI)		
			Crude	With vaccines	Without vaccines
				Number of cases = 6595	Number of cases = 6147
			Adjusted*	Adjusted*	
Oxymetholone	4	4	93.8 (48.6, 180.9)	40.4 (9.2, 178.4)	39.0 (8.0, 190.2)
Norethisterone/ethinylestradiol	5	6	78.2 (43.2, 141.4)	31.6 (9.4, 106.2)	24.9 (7.6, 82.0)
Milrinone	4	9	41.7 (20.7, 83.7)	28.2 (8.3, 95.6)	15.6 (4.7, 52.0)
Retinol	11	27	38.2 (25.0, 58.5)	53.7 (26.2, 110.2)	15.5 (7.6, 31.6)
Atazanavir	17	44	36.3 (25.7, 51.2)	33.6 (18.4, 61.4)	16.9 (9.6, 29.8)
Pemoline†	104	282	35.1 (30.5, 40.4)	31.6 (25.0, 40.0)	14.4 (11.5, 18.2)
Pyrazinamide	17	47	34.0 (24.0, 48.0)	17.0 (9.4, 30.5)	17.8 (9.9, 32.0)
Isoniazid	47	140	31.7 (25.7, 39.1)	23.5 (16.6, 33.4)	14.0 (9.9, 19.7)
Naltrexone	7	22	29.9 (17.3, 51.6)	12.8 (5.3, 31.1)	8.6 (3.6, 20.2)
Troglitazone†	10	32	29.3 (18.5, 46.4)	23.5 (11.1, 49.6)	11.3 (5.5, 23.3)
Sulthiame	8	27	27.8 (16.6, 46.6)	11.6 (5.2, 25.7)	6.1 (2.7, 13.3)
Nicardipine	4	14	26.8 (12.9, 55.8)	11.9 (3.7, 38.9)	7.0 (2.3, 21.8)
Tetrazepam	6	22	25.6 (14.0, 46.7)	5.9 (2.4, 14.6)	4.9 (2.0, 12.0)
Bosentan	85	353	22.8 (19.4, 26.9)	15.0 (11.8, 19.2)	7.3 (5.7, 9.2)
Halofantrine	4	17	22.1 (10.4, 46.8)	9.0 (3.0, 27.1)	5.3 (1.8, 15.7)
Emtricitabine	4	17	22.1 (10.4, 46.8)	14.6 (4.6, 46.0)	10.3 (3.4, 30.9)
Trimethobenzamide	4	18	20.8 (9.8, 44.4)	15.7 (5.1, 48.6)	6.3 (2.1, 18.7)
Etodolac	5	25	18.8 (9.4, 37.3)	15.8 (5.9, 42.5)	9.1 (3.4, 24.1)
Voriconazole	52	270	18.2 (14.7, 22.5)	10.7 (7.9, 14.6)	6.7 (5.0, 9.1)
Isoniazid/rifampicin	4	21	17.9 (8.2, 38.7)	7.5 (2.4, 23.2)	8.0 (2.7, 24.1)
Pioglitazone	4	21	17.9 (8.2, 38.7)	14.7 (4.9, 43.9)	6.1 (2.1, 17.9)
Codeine/pseudoephedrine	5	27	17.4 (8.7, 34.8)	6.9 (2.6, 18.2)	6.4 (2.5, 16.6)
Dapsone	9	49	17.2 (10.3, 28.9)	12.9 (6.2, 27.0)	8.5 (4.1, 17.6)
Propylthiouracil	14	79	16.6 (11.0, 25.3)	10.9 (6.1, 19.7)	7.0 (3.9, 12.6)
Gemtuzumab	42	241	16.4 (12.9, 20.9)	17.1 (12.3, 24.0)	6.8 (4.9, 9.4)
Sevoflurane	5	29	16.2 (8.0, 32.6)	13.6 (5.2, 35.5)	4.6 (1.8, 12.0)
Ursodeoxycholic acid	4	24	15.6 (7.1, 34.3)	19.9 (6.7, 58.6)	7.1 (2.4, 20.6)
Estradiol	4	24	15.6 (7.1, 34.3)	6.4 (2.1, 19.3)	4.8 (1.6, 14.0)
Mercaptopurine	41	252	15.3 (12.0, 19.6)	11.4 (8.1, 16.0)	6.0 (4.3, 8.4)
Ethinylestradiol/dienogest	7	43	15.3 (8.4, 27.7)	3.3 (1.5, 7.3)	3.0 (1.4, 6.8)
Basiliximab	26	162	15.1 (11.1, 20.6)	11.2 (7.3, 17.1)	3.8 (2.5, 5.8)
Chlorprothixene	4	25	15.0 (6.8, 33.1)	5.4 (1.9, 16.0)	3.8 (1.3, 11.0)
Dactinomycin	28	177	14.9 (11.0, 20.1)	16.7 (11.1, 20.3)	6.3 (4.2, 9.5)
Tioguanine	37	240	14.5 (11.2, 18.9)	14.2 (9.9, 20.2)	6.2 (4.4, 8.8)
Rifampicin	37	243	14.3 (11.0, 18.6)	8.4 (5.8, 12.0)	5.1 (3.6, 7.3)
Norethisterone	8	53	14.2 (8.1, 24.9)	7.4 (3.4, 15.7)	3.5 (2.9, 4.3)
Loracarbef	5	34	13.8 (6.7, 28.2)	9.1 (3.5, 23.9)	3.9 (1.5, 10.1)
Aztreonam	5	34	13.8 (6.7, 28.2)	12.3 (4.6, 32.6)	6.7 (2.6, 17.3)
Fusidic acid	8	56	13.4 (7.6, 23.7)	6.1 (2.9, 13.1)	3.5 (1.7, 7.4)
Hydroxychloroquine	6	44	12.8 (6.6, 24.7)	6.0 (2.5, 14.2)	3.9 (1.7, 9.3)
Ethosuximide	14	105	12.5 (8.1, 19.3)	8.0 (4.5, 14.2)	4.3 (2.5, 7.6)
Acetazolamide	7	54	12.2 (6.6, 22.5)	8.7 (3.9, 19.7)	4.2 (1.9, 9.3)
Nefazodone	17	136	11.7 (7.9, 17.5)	6.7 (4.0, 11.2)	4.5 (2.7, 7.4)
Levocetirizine	5	40	11.7 (5.6, 24.4)	4.4 (1.7, 11.3)	3.0 (1.2, 7.7)
Minocycline	117	959	11.6 (10.0, 13.5)	4.3 (3.5, 5.3)	3.5 (2.9, 4.3)
Josamycin	10	82	11.4 (6.8, 19.2)	5.2 (2.7, 10.1)	2.6 (1.3, 5.0)
Enoxaparin	4	33	11.4 (5.0, 25.8)	5.2 (1.8, 15.4)	3.5 (1.2, 10.0)
Paracetamol/hydrocodone	19	160	11.2 (7.6, 16.3)	4.2 (2.6, 6.8)	3.9 (2.4, 6.4)
Rasburicase	8	68	11.0 (6.2, 19.8)	5.2 (2.5, 11.0)	3.7 (1.8, 7.8)
Ethinylestradiol/gestodene	6	54	10.4 (5.3, 20.5)	2.3 (1.0, 5.5)	2.3 (1.0, 5.2)
Itraconazole	15	137	10.3 (6.7, 15.8)	4.2 (2.5, 7.3)	2.8 (1.7, 4.9)
Caspofungin	9	84	10.1 (5.8, 17.5)	4.3 (2.1, 8.6)	3.0 (1.5, 6.0)
Zafirlukast	6	56	10.0 (5.1, 19.9)	6.0 (2.6, 14.1)	3.5 (1.5, 8.1)

*Adjusted for age, gender, country of reporting and type of reporter. †Drugs withdrawn from the market due to hepatotoxicity.

Table S2Crude ROR for hepatic injury of individual drugs (with ≥ 30 cases from the main analysis) stratified by age groups

Drug	Age group <3 years			Age group 3 to 11 years			Age group 12 to 17 years		
	Number of cases	ROR With vaccines (n = 1360)	Without vaccines (n = 1104)	Number of cases	ROR With vaccines (n = 1962)	Without vaccines (n = 1882)	Number of cases	ROR With vaccines (n = 3273)	Without vaccines (n = 3161)
Isotretinoin	8	0.1*	1.8*	2	2.6*	1.1*	410	1.6	1.2
Paracetamol	117	22.6	4.0	74	5.1	2.2	156	4.9	3.6
Valproic acid	29	16.8	2.9	99	6.6	2.9	80	2.8	2.1
Carbamazepine	16	17.5	2.0	67	5.6	2.4	57	2.6	1.9
Methotrexate	13	11.2	2.0	75	8.5	3.7	46	2.6	1.9
Minocycline	-	-	-	2	5.6	2.4*	115	5.7	4.2
Lamotrigine	5	4.2	0.7*	50	3.5	1.5	57	1.8	1.3
Zidovudine	99	10.4	1.8	7	3.3	1.5*	-	-	-
Ceftriaxone	19	7.2	1.3*	56	7.3	3.2	29	3.1	2.3
Pemolinet	-	-	-	76	42.7	18.7	28	10.7	8.0
Methylphenidate	-	-	-	51	1.8	0.8*	45	1.3	0.9*
Bosentan	35	89.2	15.7	22	14.7	6.4	28	9.7	7.2
Ciclosporin	34	31	5.4	23	3.8	1.7	14	1.6	1.2*
Atomoxetine	-	-	-	17	1.7	0.7*	47	2.9	2.1
Azithromycin	10	2.8	0.5*	30	1.9	0.8*	23	1.3	1.0*
Olanzapine	-	-	-	5	2.4	1.0*	57	4.2	3.1
Infliximab	-	-	-	4	0.8*	0.3*	56	1.6	1.2*
Erythromycin	12	7	1.2*	30	4.9	2.1	18	3.0	2.3
Risperidone	-	-	-	20	2.1	0.9*	39	1.0	0.7*
Phenytol	11	12.1	2.1	18	4.0	1.7	28	2.0	1.5
Voriconazole	4	67.5	11.8	19	14.6	6.4	29	9.3	6.9
Topiramate	11	11.6	2.0	23	3.3	1.4*	17	1.5*	1.1*
Sulfamethoxazole/trimethoprim	8	2	0.3*	13	0.9	0.4*	27	1.4	1.0*
Isoniazid	8	10.2	10.7	15	30.0	13.1	24	16.3	12.1
Vincristine	12	15.7	2.8	21	3.5	1.5	13	1.4*	1.0*
Lamivudine	25	10.7	1.9	17	7.8	3.4	3	2.6*	1.9*
Ethinylestradiol/levonorelrel	-	-	-	-	-	-	43	2.1	1.6
Oxcarbazepine	5	10.3	1.8*	13	2.2	0.9*	25	2.0	1.5
Fluconazole	13	14.6	2.6	7	5.9	2.6	22	9.3	6.9
Gemtuzumab	1	4.2	0.7*	27	16.4	7.2	14	15.6	11.6
Mercaptopurine	2	17.5	3.1*	16	11.1	4.8	23	10.6	7.9
Phenobarbital	11	11.5	2.0	22	8.3	3.6	8	2.5	1.8*
Amoxicillin/clavulanate potassium	9	4.8	0.8*	12	1.8	0.8*	17	2.7	2.0
Rifampicin	11	43.3	7.6	11	17.0	7.4	15	5.2	3.9
Tioguanine	3	34.6	6.1	28	15.5	6.8	6	4.6	3.4
Nevirapine	29	5.3	0.9*	3	1.9*	0.8*	5	1.8*	1.4*
Clozapine	-	-	-	1	1.0*	0.4*	35	1.1	0.8*
Cytarabine	10	15.6	5.7	16	3.1	1.4*	10	1.6*	1.2*
Clarithromycin	6	7.3	1.3*	13	2.4	1.1*	16	1.7	1.2*
Acetylsalicylic acid	2	2.6	0.5*	15	3.4	1.5*	13	1.1*	0.8*
Interferon beta	-	-	-	20	13.4	5.9	10	1.5*	1.1*

*Not statistically significant crude RORs. †Drugs have been ranked by number of cases. Topical drug-related records have been excluded.