A Systematic Review of Substandard, Falsified, Unlicensed and Unregistered Medicine Sampling Studies

APPENDICES

Appendix, table 1: Strategy for literature search one (Substandard and falsified medicines)

No.	Search term(s)	Number of publications identified		
		Embase	**MEDLINE**	**PubMed**
1	Counterfeit	1089	471	643
2	Fake	823	444	709
3	Substandard	1055	513	708
4	Falsified	439	200	294
5	**1 or 2 or 3 or 4**	2975	1419	2076
6	Drug	2897296	531988	1227254
7	Medicine	3130772	1614444	2031416
8	Pharmaceutical	293223	158914	377926
9	Antimicrobial	91971	55290	335249
10	Antimalarial	10761	6930	16140
11	Antibiotic	209851	48171	156407
12	**6 or 7 or 8 or 9 or 10 or 11**	5016630	2047399	3013641
13	**5 and 12**	1943	738	1035

Appendix, table 2: Strategy for literature search two (Unlicensed and unregistered)

No.	Search term(s)	Number of publications identified		
		Embase	**MEDLINE**	**PubMed**
1	Counterfeit	1089	471	642
2	Fake	823	444	709
3	Substandard	1055	513	709
4	Falsified	439	200	294
5	Unregistered	339	184	239
6	Unlicensed	925	384	505
7	**1 or 2 or 3 or 4 or 5 or 6**	4197	1973	2798
8	Drug	2897296	531988	1224895
9	Medicine	3130772	1614444	2030100
10	Pharmaceutical	293223	158914	377583
11	Antimicrobial	91971	55290	334384
12	Antimalarial	10761	6930	16114
13	Antibiotic	209851	48171	156079
14	**8 or 9 or 10 or 11 or 12 or 13**	5016630	2047399	3011030
15	**7 and 14**	2846	1065	1500

Appendix, table 3: Data extraction of the 33 studies to pass quality assessment (Substandard and falsified)

Country [Reference]	Drugs (n=number of various products tested)	Setting	Formulation studied	Labeled origin	Method of testing/location	Stated problems	% (substandard or falsified)	Methodological strength scoring (0-12)
The prevalence of falsified and substandard medicines in low-income countries								
Malawi[1]	Antibiotics and antimalarial drugs, artemether/lumefantrine, sulfadoxine/pyrimethamine, quinine hydrochloride, phenoxymethylpenicillin, amoxicillin, artesunate/amodiaquine, quinine sulphate, ciprofloxacin, amoxicillin/clavulanic acid, chloramphenicol, dihydroartemisinin/piperaquine, cefuroxime (n=155)	Public outlets	Tablets, capsules and injectables	India, Kenya, China, USA, Malawi, Morocco, Tanzania, Cyprus, Austria, Switzerland, UAE, unknown	Thin-layer-chromatography, HPLC, disintegration testing / University of Malawi; Nairobi, Kenya	No active ingredient, inadequate active ingredient quantity, wrong active ingredient, dissolution failure	1.5% (6/155 substandard, 1/155 falsified)	10
Malawi[2]	Antimalarial drugs, Artemisinin and non-artemisinin based treatments (n=112)	Public, private and informal outlets	Tablets	Local and imported	Semi-quantitative TLC, HPLC / Department of Chemistry, University of Ghana, Legon, Accra, Ghana	Inadequate active ingredient quantity, excessive active ingredient quantity	88.4% (substandard)	10
Tanzania[3]	Antimalarial drugs, artemisinin combination therapy, artemisinin, artesunate, artemether, dihydroartemisinin, dichlorodihydrate (n=1737)	Private outlets	Tablets, oral suspensions, injectables	Local and imported	HPLC, ultraviolet photo-diode array detection / Center for Disease Control Atlanta, GA; Georgia Institute of Technology, Atlanta, GA; London School of Hygiene and Tropical Medicine	Inadequate active ingredient quantity	12.1% (substandard)	9

Ethiopia[4]	Antihelminthic drugs (mebendazole, albendazole), antiprotozoal drugs (tinidazole) (n=106)	Public and private outlets	Tablets	China, Ethiopia, India, Kenya, Cyprus, Korea	HPLC, ultraviolet photo-diode array detection / Jimma University Laboratory of Drug Quality (JuLaDQ), Ethiopia	Inadequate active ingredient quantity, excessive active ingredient quantity, dissolution failure	45.3% (substandard)	11
Nepal[5]	Various; paracetamol, cloxacillin, amlodipine, metformin, losartan, cefixime, ofloxacin, carbamazepine (n=40)	Public and private outlets	Tablets and capsules	Local and imported	Comparison to control parameters: physical standard, identification, assay, disintegration, dissolution tests	Inadequate active ingredient quantity, dissolution test failure	32.5% (substandard)	6
Afghanistan[6]	Antimalarial drugs (n=134)	Public and private outlets	Tablets, syrups, injectable solutions	Local and imported	HPLC-UV-PDA / London School of Hygiene and Tropical Medicine	Disintegration, dissolution, content uniformity test failure.	26% (substandard)	10
Togo[7]	Various, including antibiotics, antidiabetics, cardiac drugs and antiasthmatic drugs (n=92)	Private and informal outlets	Tablets	Africa, Asia and Europe	Visual inspection, HPLC, thermal degradation	Inadequate/excessive active ingredient quantity	11%	10
The prevalence of falsified and substandard medicines in lower-middle-income countries in Asia and Africa								
Cambodia[8]	Antibiotics, (cefixme, clarithromycin), omeprazole, co-trimoxazole, sildenafil (n=325)	Private outlets	Tablets and capsules	Local and imported	HPLC, ultraviolet spectrophotometry, mass uniformity analysis, dissolution test / Shimadzu, Kyoto, Japan	Inadequate active ingredient quantity, mass uniformity and dissolution failure	43.7% (substandard)	11
Cambodia[9]	Antimalarial drugs, artesunate, artesunate + mefloquine, artemether, artemisinin/piperaquine, dihydroartemisinin/piperaquine, dihydroartemisinin (n=291)	Private outlets	Tablets and injectables	Local and imported	HPLC, ultraviolet photo-diode array detection / Center for Disease Control Atlanta, GA; Georgia Institute of Technology, Atlanta, GA; London School of Hygiene and Tropical Medicine	Inadequate active ingredient quantity	31% (substandard)	10

Cambodia[10]	Antibiotics, amoxicillin-clavulanic acid (n=59)	Private outlets	Tablets	Local and imported	HPLC, spectrophotometric testing / Department of Drug Management and Policy, Kanazawa University, Japan	Inadequate active ingredient quantity, content uniformity, dissolution test failures	64.4% (substandard)	11
Lao PDR[11]	Antimalarial drugs, artesunate, chloroquine, quinine dihydrochloride, artemetherlumefantrine (n=146)	Private outlets	Tablets, injectables and syrups	Thailand, France, Vietnam, USA, unknown	HPLC, mass spectroscopy / Center for Disease Control Atlanta, GA; Georgia Institute of Technology, Atlanta, GA; London School of Hygiene and Tropical Medicine	Inadequate active ingredient quantity	25.4% (substandard)	9
Nigeria [12]	Antimalarial drugs, artemisinin combination therapy, artemisinin monotherapy (n=3024)	Public, private and informal outlets	Tablets, capsules, oral suspensions, injectables	Local and imported	HPLC, mass spectroscopy, ultraviolet photo-diode array detection / London School of Hygiene and Tropical Medicine	No active ingredient, inadequate active ingredient quantity	9.3% (6.8% substandard, 1.3% degraded and 1.2% falsified)	11
Nigeria[13]	Oxytocin, misprostol, magnesium sulfate, calcium gluconate (n=637)	Public outlets	Tablets, injectables	China, India, Germany	HPLC / not stated	Inadequate active ingredient quantity	30% (substandard)	11
Nigeria[14]	Anti-hypertensive medicines - Amlodipine and Lisinonpril (n=440)	Public outlets	Not stated	Local and imported	HPLC / not stated	Inadequate active ingredient quantity	32% (substandard)	6
Kenya[15]	Various; Antibiotics, antihistamines, NSAIDs (n=60)	Public and private outlets	Tablets, capsules and rehydration salts	Local and imported	HPLC, UV spectroscopy / Kenya National Quality Control Laboratory, Nairobi, Kenya	Inadequate active ingredient quantity, dissolution test failure	17% (substandard or falsified)	9

Kenya[16]	Antimalarial drugs, artemisinin combination therapy (n=39)	Public and private outlets	Tablets	Local and imported	HPLC, UV spectroscopy / Drugs and Analysis Research unit, University of Nairobi, Nairobi, Kenya	None	0% (substandard)	7
Ghana[17]	Antimalarial drugs, artesunate, amodiaquine therapy (n=16)	Private outlets	Tablets	Local and imported	Qualitative colourmetric testing, HPLC, spectrophotometric testing / Department of Immunology, Noguchi Memorial Institute for Medical Research, Legon, Accra, Ghana	Inadequate active ingredient quantity	6.3% (substandard)	11
Ghana[18]	Antimalarial drugs, artemisinin combination therapy, artemisinin, artesunate, artemether, dihydroartemisinin, amodiaquine dichlorodihydrate and pyrimethamine (n=254)	Public, private and informal outlets	Tablets	Local and imported	HPLC, mass spectroscopy, ultraviolet photo-diode array detection / Georgia Institute of Technology, Atlanta, GA; London School of Hygiene and Tropical Medicine	Inadequate active ingredient quantity	35.4% (substandard)	11
Ghana[19]	Antibiotics, antimalarials, antihelmintics, antifungals, analgesics (n=68)	Public and private outlets	Tablets and other formulations1	United Kingdom, South Africa, local	HPLC, ultraviolet spectrophotometry	Inadequate active ingredient quantity	62% (substandard)	9

Ghana and Nigeria[20]	Antibiotics, azithromycin, erythromycin, clindamycin (n=45)	Unknown	Tablets, capsules and oral suspensions	India, Ghana, England, Romania, Bangladesh, Italy, Nigeria, Ecuador, China, Malaysia, Pakistan, France	HPLC, ultraviolet spectrophotometry, dissolution test, US Pharmacopoeia requirements were used / Department of Chemistry and School of Pharmacy, University of Ghana, Legon	Inadequate active ingredient quantity	73% (substandard)	8
Mongolia[21]	Antibiotics and antimicrobials, (ampicillin, amoxicillin, co-trimoxazole, metronidazole, doxycycline, nystatin), analgesics (paracetamol and ibuprofen), bromhexin (n=1236)	Public and private outlets	Tablets and capsules	China, Mongolia, UK	Thin-layer-chromatography, ultraviolet spectrophotometry / School of Pharmacy, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia	Inadequate active ingredient quantity, dissolution failure	14.6% (substandard)	11
Myanmar[22]	Antimalarial drugs (n=153)	Public and private outlets	Tablets and capsules	Local and imported	HPLC, UV spectroscopy / College of Agronomy and Biotechnology, China Agricultural University, Beijing, China	No active ingredient present	0.7% (falsified)	9
The prevalence of falsified and substandard medicines in upper-middle-income countries in Asia and Africa								

Gabon [23]	Antimalarial drugs, artemether-lumefantrine, artesunate, amodiaquine, sulfadoxine, dihydroartemisinin-piperaquine, dihydroartemisinin-piperaquine-trimethoprim, artemisinin-piperaquine, artemisinin-naphtoquine, quinine, sulfadoxine-pyrimethamine, mefloquine, proguanil, atovaquone-proguanil, proguanil-chloroquine, pyrimethamine, chloroquine (n=432)	Public, private and informal outlets	Tablets	India, China, Ivory Coast, Switzerland, Germany, Italy, Morocco, Greece, Luxembourg, Canada, UK, Spain, France	HPLC, thin-layer chromatography, ultraviolet photo-diode array detection / London School of Hygiene and Tropical Medicine; Utrecht University, Netherlands	No active ingredient, inadequate active ingredient quantity	0.5% (substandard)	11
Kazakhstan[24]	Anti-tuberculosis drugs (n=854)	Public outlets	Various, including tablets and liquid forms	Kazakhstan, India, Russia	Dissolution test, semi-quantitative thin-layer chromatography / not stated	Packaging test failure, Inadequate active ingredient quantity, dissolution test failure	19% (substandard)	11
South Africa[25]	Antibiotics (amoxicillin), Analgesics (paracetamol) (n=316 samples)	Public and private outlets	Tablets	Local and imported	Dissolution test, content uniformity test, HPLC, UV /	Packaging test failure, inadequate active ingredient quantity, dissolution test failure	55.4% substandard	12
The prevalence of falsified and substandard medicines in the mixed group								
Benin, Burkina-Faso, Congo-Brazzaville, the Democratic Republic of Congo, Guinea, Côte d'Ivoire, Mauritania, Niger, Togo and Senegal[26]	Cardiovascular medications, anticoagulants (acenocoumarol), anti-hypertensives, furosemide, hydrochlorothiazide (diuretics), captopril (angiotensin-converting- enzyme inhibitor), atenolol (beta-blocker) and amlodipine (calcium channel blocker), Statins (simvastatin) (n=3468)	Private and informal outlets	Tablets and capsules	Europe, Asia, Africa, unknown	Reversed-phase liquid chromatography with tandem mass spectrometry / Department of Laboratories, Paris	Inadequate active ingredient quantity	16.3% (substandard)	12

Angola, Brazil, China, Democratic Republic of Congo, Egypt, Ethiopia, Ghana, India, Kenya, Nigeria, Russia, Rwanda, Thailand, Turkey, Uganda, United Republic of Tanzania and Zambia[27]	Anti-tuberculosis drugs (n=713)	Public, private and informal outlets	Not stated	Not stated	Thin-layer chromatography, HPLC, GPHF mini-lab/ Various locations	Inadequate active ingredient quantity, dissolution test failure	9.1% (substandard)	8
Ghana, Nigeria, United Kingdom[28]	Antibiotics, amoxicillin and co-trimoxazole (n=35)	Public, private and informal outlets	Tablets	China, Ghana, India, Ireland, Nigeria, and United Kingdom	Thin-layer chromatography, HPLC / London School of Hygiene and Tropical Medicine	Inadequate active ingredient quantity	26% (substandard)	8
Kenya and Gabon[29]	Anti-epileptic drugs (n=61)	Public, private and informal outlets	Not stated	Local and imported	Active ingredients assay, related substances screening, mass uniformity, dissolution, disintegration and friability, MS and NMR / Not stated	Inadequate active ingredient quantity, No active ingredient present	5% (substandard or falsified)	7
Cambodia, Indonesia, Laos, Myanmar, Singapore, Thailand, and Vietnam[30]	Antimalarial drugs and antibiotics (n=188)	Public, private and informal outlets	Various including tablets and capsules	Local and imported	HPLC, Fourier transform infrared spectroscopy / Pharmaceutical laboratory Health Sciences Authority (HSA), Singapore	Inadequate active ingredient quantity, excessive active ingredient quantity	31% (substandard)	8

Cameroon, DR Congo, Nigeria, Kenya, Uganda, Ghana, India[31]	Various; predominantly anti-infectives (n=869)	Public, private and informal outlets	Tablets and capsules	India, China, Kenya, Ghana, Nigeria, Uganda, DR Congo, Cameroon, South Africa, UK, Germany, France, Netherlands, Cyprus, Italy, Spain, Switzerland, Belgium, Poland	TLC, HPLC, UV spectroscopy, GPHF Minilab / Department of drug administration, National medicine laboratory, Nepal	Inadequate active ingredient quantity, no active ingredient present, dissolution test failure	2.4% (substandard or falsified)	8
Benin, DR Congo, Rwanda[32]	Antimalarial drugs (n=34)	Private and informal outlets	Tablets, capsules and rehydration salts	Local and imported	TLC, HPLC, Raman spectroscopy / not stated	Insufficient API quantity, dissolution test failure, impurities present	2.9% (substandard)	9
Gabon, Kenya, Madagascar[33]	Antiepileptic drugs (n=3782)	Public, private and informal outlets	Tablets and other formulations	China, India, European union (unspec.), Senegal, local	HPLC / not stated	Insufficient API quantity	32.3% (substandard)	9

Appendix figure 1: Geographical spread of countries in which prevalence studies on substandard and falsified medicines took place.

Appendix table 4: Data extraction of the 47 studies on the prevalence of Unlicensed and unregistered medicines

Country [Reference]	Drugs (n=number of prescriptions/patients surveyed)	Setting	Formulation studied	Labeled origin	Study type/location	% (unlicensed or unregistered)
The prevalence of unlicensed and unregistered medicines in high-income countries						
Australia [34]	Various therapeutic classes, including: alimentary tract and metabolism, cardiovascular system, dermatologicals, genito-urinary system and sex hormones, systemic hormonal preparations excl. sex hormones, anti-infectives, antineoplastics and immunomodulating agents, musculo-skeletal system, nervous system, anti-parasitic products, insecticides and repellent, respiratory system, sensory organs (n=2654 prescriptions)	Paediatric teaching hospital	Not stated	Not stated	12 month retrospective study / Princess Margaret Hospital, Western Australia	2.6% of prescriptions were unlicensed
Australia [35]	Various drugs, including: salbutamol, ondansetron, ipratropium, fentanyl and oxycodone (n=6786 prescriptions)	Paediatric emergency departments of 6 teaching hospitals	Various, including tablets and oral solutions	Not stated	12 month retrospective observational study / Austin Hospital, Royal Childrens Hospital, Murdoch Childrens Research Institute, Monash Medical Centre, Dandenong Hospital, Sunshine Hosptial; Melbourne, Victoria, Australia	36.3% of prescriptions were unlicensed/off-label
Canada[36]	Various drugs, including: Morphine sulphate, Salbutamol, Polyethylene, glycol, Lansoprazole, Diphenhydramine, Dimenhydrinate, Piercailline + tazobactam, Ondansetron, Metoclopramide, Hydrocortisone, Fentanyl, Ranitidine, Furosemide, Acetaminophen, Lorazepam, Hydromorphone, Pentamidine, Midazolam, Trimethoprim + sulfamethozaxol, Nystatin (n=2145 prescriptions)	Maternity-paediatric tertiary care hospital	Various, including tablets and oral solutions	Not stated	24 hour, cross sectional study / Division of Emergency Medicine, Department of Pediatrics, CHU Sainte-Justine, Montreal, Quebec	8.3% of prescriptions were unlicensed
Canada[37]	Intravenous Immunoglobulin (IVIG), indications included: secondary immunodeficiency, ITP, Kawasaki disease, primary immunodeficiency and Guillain-Barre Syndrome (n=54 patients)	Tertiary care pediatric centre	Not stated	Not stated	6 month observational study / Children's Hospital of Eastern Ontario, Ottawa, Canada	56% of prescriptions were for unlicensed indications

Spain [38]	Various therapeutic classes, including: nervous system therapy, cardiovascular system and digestive system (n=696 prescriptions)	Paediatric intensive care unit	Not stated	Not stated	6 week observational, descriptive, prospective pilot study / Hospital Infantil Universitario Niño Jesús, Madrid, Spain	8.9% of prescriptions were unlicensed
Spain[39]	Various drugs including: Ampicillin, gentamycin, midazolam, furosemide, dopamine, cefotaxime, metamizol, fentanyl, vancomycin and methylprednisolone (n=601 prescriptions)	Neonatal and pediatric intensive care unit	Various, including tablets and oral solutions	Not stated	Prospective observational study / Hospital Axarquia, Velez Malaga, Spain	5% of prescriptions were unlicensed
Spain[40]	Various therapeutic classes, including: Anti-infectives, Nervous system, Alimentary tract and Metabolism, and others (n=273 prescriptions)	Neonatal intensive care unit	Various, including tablets and oral solutions	Not stated	3 months observational, restrospective study / La Arriixacata Hospital, Spain	5% of prescriptions were unlicensed
Italy[41]	Cardiovascular drugs, central nervous system drugs, gastrointestinals and anti-infectives (n=720 prescriptions)	Neonatal intensive care units	Various including injectables	Not stated	1-day survey via an online questionnaire / all 107 level III Italian neonatal intensive care units.	14.5% of prescriptions were unlicensed
Italy[42]	Variosu therapeutic classes, including: Cardiovascular drugs, central nervous system drugs, gastrointestinals and anti-infectives (n-483 prescriptions)	Neonatal intensive care units	Various including injectables	Not stated	1 month observational study / Southern Italy	11.4% of prescriptions were unlicensed
Italy[43]	Proton pump inhibitors (n=260 patients)	Community pharmacies	Various, including tablets and oral solutions	Not stated	3 month cross sectional study / 8 community pharmacies across Italy	48% of prescriptions were unlicensed
Czech Republic [44]	Various therapeutic classes, including: ACE inhibitors, antihistamines, bronchodilators (n=8559 prescriptions)	Paediatric department, general hospital	Various, including tablets and oral solutions	Not stated	6 month retrospective study / University Hospital Olomouc, Czech Republic	1.3% of prescriptions were unlicensed
France [45]	Various therapeutic classes, including: Alimentary tract, metabolic and nervous system (n=315 prescriptions)	Maternity-paediatric university hospital	Various, including: tablets, capsules and injectables	Not stated	1 day retrospective, cross-sectional study / Paris, France (hospital not stated)	3.2% of prescriptions were unlicensed
France[46]	Antibiotics (n=108 prescriptions)	Maternity-paediatric university hospital	Various, including: tablets, capsules and injectables	Not stated	Observational study / Lyon, France	0% of prescriptions were unlicensed

France[47]	Anti-epileptic drugs (n=not stated)	Paediatric tertiary referral centre	Not stated	Not stated	Retrospective study / Necker Enfants Malades Hospital, France	26% of prescriptions were unlicensed
France[48]	Various drugs, including: Tixocortol, tuaminoheptane, mequitazine, desloratadine, amoxicillin (n=1960 patients)	Paediatric Outpatients, General Hospitals	Various, including: tablets, capsules and injectables	Not stated	5 month observational study / Southwestern France	6.7% of prescriptions were unlicensed
France[49]	Various therapeutics classes, including: Antibiotics, CNS drugs, Vitamins (n=8891 prescriptions)	Neonatal intensive care units of university hospitals	Not stated	Not stated	12 month prospective study / France	5.2% of prescriptions were unlicensed
Finland[50]	Various drugs, including: Paracetamol, ibuprofen, fentanyl, salbutamol, midazolam, oxycodone, sevoflurane, caffeine, fluconazole (n=1054)	Neonatal intensive care unit, general paediatric ward and paediatric surgical ward	Various, including: tablets, oral solutions and injectables	Not stated	2 week prospective study / Kuopio University Hospital, Finland	79% of patients received at least one unlicensed medication
Malta[51]	Not stated (n=209 prescriptions)	Not stated	Not stated	Not stated	Prospective longitudinal cohort study / Malta	54.1% of prescriptions were unlicensed/off-label
Malta[52]	Various therapeutic classes, including: Alimentary tract and metabolism, blood and blood-forming organs, cardiovascular system, systemic hormonal preparations, anti-infectives for systemic use, antineoplastic and immunomodulating agents, musculo-skeletal system, nervous system, respiratory system, sensory organs (n=1507 prescriptions)	Paediatric, primary care	Not stated	Not stated	Prospective observational study / Malta	3.3% of prescriptions were unlicensed
Netherlands[53]	Various drugs, including: Benzyl-penicillin, gentamycin, caffeine, morphine and surfactant (n=24903 prescriptions)	Neonatal intensive care unit	Not stated	Not stated	Retrospective study / Hospital not stated, Netherlands	8% of prescriptions were unlicensed

Norway [54]	Various therapeutic classes, including: Alimentary tract and metabolism, blood and blood-forming organs, cardiovascular system, systemic hormonal preparations, anti-infectives for systemic use, antineoplastic and immunomodulating agents, musculo-skeletal system, nervous system, respiratory system, sensory organs (n=930 prescriptions)	University hospital, paediatrics unit	Various, including: tablets, oral solutions and injectables	Not stated	3 month prospective, cross-sectional study / Oslo University hosipital, Ulleval, Akershus University hospital; Norway	26% of prescriptions were unlicensed
Norway[55]	Not stated	University hospital	Various, including: tablets, oral solutions and injectables	Not stated	5 week retrospective study / Oslo University Hospital, Ulleval, Norway	32% of prescriptions were unlicensed
Republic of Ireland[56]	Various drugs, including: Gentamycin, Vitmain K, Benzylpeneiillin, Morphine Sulphate, Caffeine citrate, Phenylephrine, Cyclopentolate (n=69 drug types)	Neonatal intensive care unit	Various, including: tablets, oral solutions and injectables	Not stated	2 month prospective study / The National Maternity Hospital, Dublin, Ireland	19% of drugs were unclicensed
United Kingdom[57]	Various drugs, including: Metronidazole, Gentamicin, Spironolactone, Chloral hydrate, Diclofenac, Ondansetron, Dexanethsone, Ibuprofen, Melatonin, Folic acid, Morphine sulphate, Paracetamol, Salbutamol (n= 16551 courses)	Paediatric tertiary referral centre	Various, including: tablets, oral solutions and injectables	Not stated	12 month prospective observational study / Alder Hey Children's NHS Foundation Trust	5.4% of prescriptions were unlicensed
United Kingdom[58]	Various drugs, including: Cefuroxime, Cefotaxime, Chlorphenamine, Diazepam, Ibuprofen, Lactulose, Cefalexin, Metronidazole, Furosemide, Furosemide, Ondansetron, Salbutamol, Ranitidine, Dexamethasone, Fentanyl, Morphine, Diclofenac, Codeine Phosphate (n=10669 prescriptions)	Paediatric hospital	Various, including: tablets, oral solutions and injectables	Not stated	12 month prospective observational study / Alder Hey Children's NHS Foundation Trust	7.5% of prescriptions were unlicensed
United Kingdom[59]	Antipsychotic drugs (n=50 patients)	Community mental health patients	Various, including: tablets, oral solutions and injectables	Not stated	1 year study / Herefordshire, South England	17.5% of prescriptions were unlicensed

Slovak Republic[60]	Various drugs, including: Cholecalciferol, Phytomenadione, Ketoconazole[ATC/DDD] Gentamicin[ATC/DDD] Anti-diarrheal microorganisms, Ampicillin Pyridoxine, Folic acid, Clotrimazole, Phenobarbital (n=962 prescriptions)	Paediatric hospital	Various, including: tablets, oral solutions and injectables	Not stated	6 month cross sectional study / Pathological Newborns of Children's University Hospital, Bratislava, and Unit of Pathological Newborns of Teaching Hospital Nitra, Slovak Republic	4.8% of prescriptions were unlicensed
The prevalence of unlicensed and unregistered medicines in upper-middle-income countries						
Lebanon[61]	Various therapeutic classes including: Alimentary tract and metabolism, Blood and blood-forming organs, Cardiovascular system, Genitourinary system and sex hormones[ATC/DDD] Anti-infective agents for systemic use, Antineoplastic and immune-modulating agents, Musculoskeletal system, Nervous system, Respiratory system, Sensory organs (n=2053 prescriptions)	Paediatric ICU, University hospital	Various, including: tablets, oral solutions and injectables	Not stated	Retrospective analysis / Hˆotel-Dieu de France Hospital, Saint-Joseph University of Beirut	15.8% of prescriptions were unlicensed
Malaysia[62]	Various drugsm including: Ferric ammonium citrate and folic acid (n=1295 prescriptions)	Paediatric and neonatal ICU, University hospital	Various, including: tablets, oral solutions and injectables	Not stated	2 month prospective, observational exploratory study / Universiti Kebangsaan Malaysia Medical Centre, Malaysia	27.3% of prescriptions were unlicensed
Malaysia[63]	Various therapeutic classes (n=888 medical products)	Multiple public outlets	Various	Not stated	12 month cross sectional retrospective study / Malaysia	0.45% of products were unregistered
Brazil [64]	Antiepileptics, Phenobarbital, Phenytoin, Carbamazepine, Valproic acid, Clonazepam, Diazepam, Topiramate, Lorazepam, Clobazam, Vigabatrin, Lamotrigine, Oxcabazepine, Nitrazepam, Levetiracetam, Divalproex, Gabapentin, Sulthiame (n=583 patients)	General hospital	Tablets, injectables and oral solutions	Not stated	Cross-sectional, retrospective and observational study / General Hospital of the Faculty of Medicine at Ribeirao Preto, Brazil	53.8% of patients prescribed a drug were given an unlicensed drug
Brazil[65]	Various drugs, including: Acetaminophen and dipyrone (n=1328 prescriptions)	Paediatric nursery, general hospital	Not stated	Not stated	Observational, transversal and restrospective study/ UFRGS-HCPA, Paediatrics service, Porto Alegre, Brazil	28% of prescriptions were unlicensed

Brazil[66]	Various drugs, including: Metamizole, omeprazole, captopril, fenoterol, ranitdine, ceftriaxone (n=1158 prescriptions)	Pediatric hospital	Not stated	Not stated	6 month descriptive, prospective and cross-sectional study / Instituto de Saúde da Criança do Amazonas, Manaus, Amazonas. Brazil.	6.3% of prescriptions were unlicensed
Brazil[67]	Various drugs, including: Aminophylline, Phytomenadione, Multivitamins, Folinic acid, Ampicillin, Gentamicin, Fentanyl, Heparin, Pulmonary surfactant, Meropenem, Vancomycin, Dobutamine, Amphotericin B, Cefepime, Domperidone, Telcoplanin, Epinephrin, Triaculum Phosphate, Rainitidine, Femous Sulfate (n=3290 prescriptions)	Neonatal intensive care unit	Various including injectables and oral solutions	Not stated	6 month retrospective study / Mother and Child Hospital of Brasilia, Brasilia, Brazil	12% of prescriptions were unlicensed
Brazil[68]	Various therapeutic classes, including: Alimentary tract and metabolism, immunosuppresants, antithrombotic agents, antivirals for systemic use, antiepileptics, lipid-modifying agents, antineoplastic agents (n=614 drug purchases)	Federal database	Various including injectables and oral solutions	Not stated	Longitudinal study / Brazilian Federal Government database, Brazil	0.1% of prescriptions were unlicensed
Brazil[69]	Various therapeutic classes including: Alimentary tract and metabolism, immunosuppresants, antithrombotic agents, nervous system, anti-parasitics (n=3935 prescriptions)	Neonatal intensive care unit	Various including injectables and oral solutions	Not stated	Prospective cohort study / School Maternity Januário Cicco, Health Sciences Centre, Universidade Federal do Rio Grande Norte, Natal, RN, Brazil	24.6% of prescriptions were unlicensed
Romania[70]	Various therapeutic classes, including: anti-infectives for systemic use, alimentary tract and metabolism, nervous system, and respiratory system (n=100 patients)	Paediatric unit, teaching hospital	Various including tablets, injectables and oral solutions	Not stated	Observational and retrospective study / paediatrics Clinic 3, Cluj-Napoca, Romania	6.2% of patients prescribed a drug were given an unlicensed drug
Israel[71]	Various therapeutic classes (n=1064 prescriptions, 49 medications)	Neonatal intensive care unit, paediatric intensive care unit	Various	Not stated	2 month observational study / Assaf Harofeh Medical Center, Tel-Aviv, Israel	5.9% of prescriptions were unlicensed, 64.8 off-label

Saudi Arabia[72]	Various therapeutic classes (n=583 prescriptions)	Neonatal intensive care unit	Various	Not stated	3 month prospective cohort study / King Fahd Medical Military Medical Complex, Dhahra	12.9% of prescriptions were unlicensed, 29.7% off label
South Africa[73]	Various drugs, including: HIV therapies (n=2402 prescriptions)	Ambulatory clinics	Various including tablets, injectables and oral solutions	Not stated	3 month prospective study / Tygerberg hospital, Cape Town, South Africa	2.7% of drugs prescriptions were unlicensed
South Africa[74]	Various drugs, including: Penicillin, Gentamycin, Aminophylline, Meropenem, Vancomycin, Phenobarbitone, Paracetamol, Tilidine, Vitamin K Glycerine suppository (n=759 medicines implicated in ADRs)	Neonatal intensive care unit	Various including tablets, injectables and oral solutions	Not stated	3 month prospective study / Tygerberg hospital, Cape Town, South Africa	12% of drugs prescriptions were unlicensed
The prevalence of unlicensed and unregistered medicines in lower-middle-income countries						
Mongolia [21]	Antimicrobials, (ampicillin, amoxicillin, co-trimoxazole, metronidazole, doxycycline, nystatin), analgesics (paracetamol and ibuprofen), bromhexin (n=1236)	Public and private outlets	Tablets and capsules	China, Mongolia, UK	Field study / 4 districts in Ulaanbaatar (Chingeltei, Khan-Uul, Bayanzurkh, and Songinokhair), 4 rural provinces (Bayan-Uglii, Dornogobi, Selenge, and Umnugobi), Mongolia	17.7% of drugs collected were unregistered.
India [75]	Various drugs, including: Adrenaline, nor-adrenaline, Frusemide, Oseltamavir, Cefepime, Aminoven, Acetazolamide, Flucanazole, Nifedepine, Levetiracetam, Ceftriaxone, Clobazam (n=1790 prescriptions)	Paediatric intensive care units	Various including tablets, capsules and intravenous formulations	Not stated	12 month prospective observational study / Department of Paediatrics, TN Medical College and BYL Nair Charitable Hospital, Mumbai, India	21% of prescriptions were unlicensed
India [76]	Various therapeutic classes, including: antibiotics, pain relief, anti-infectives and anti-emetics. (n=405 prescriptions)	Tertiary care teaching hospital	Not stated	Not stated	Prospective observational study / Hospital not stated	0.2% of prescriptions were unlicensed
India[77]	Neurological therapies, including: Oxcarbazepine, Sertraline, Lorazepam, Alprazolam, Topiramate, Risperidone (n=140 prescriptions)	Tertiary care teaching hospital	Various including tablets, capsules and intravenous formulations	Not stated	2 month prospective study / Hospital not stated	3.6% of prescriptions were unlicensed
Indonesia [78]	Various therapeutic classes, including: cardiovascular, antineoplastic and immunomodulating agents (n=1553 prescriptions)	Paediatric unit, teaching hosptial	Not stated	Not stated	12 month retrospective study / Cipto Mangunkusumo Hospital, Jakarta, Indonesia	15.1% of prescriptions were unlicensed

Pakistan [79]	Various therapeutic classes, including: anti-infective agents for systemic use, musculoskeletal system, alimentary tract and metabolism (n=3168 prescriptions)	Paediatric surgical units, tertiary care hospitals	Not stated	Not stated	12 month observational study / Lady Reading Hospital, Khyber Teaching Hospital, Northwest General Hospital; Peshawar, Pakistan	64.9% of prescriptions were unlicensed

Appendix figure 2: Geographical spread of countries in which prevalence studies on unlicensed and unregistered medicines took place.

Studies included in this review

1. Khuluza F, Kigera S, Heide L. Low Prevalence of Substandard and Falsified Antimalarial and Antibiotic Medicines in Public and Faith-Based Health Facilities of Southern Malawi. Am J Trop Med Hyg. 2017 May;96(5):1124–35.
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