**Supplemental Digital Content 1.** Search strategy

**Database:**

**Medline - Ovid 1946 to February 2020**

**Database:**

**Embase – Ovid 1974 to February 2020**

1. exp prescription drug misuse/

2. antibiotic resistance/

3. antimicrobial stewardship/

4. "drug utilization review"/

5. exp \*anti-infective agent/ae, ad, do, dt, pe [Adverse Drug Reaction, Drug Administration, Drug Dose, Drug Therapy, Pharmacoeconomics]

6. clinical practice/

7. exp inappropriate prescribing/

8. health service/

9. protocol compliance/

10. prescription/

11. (1 or 4 or 6 or 7 or 8 or 10) and 5

12. 5 and 9

13. 5 and (6 or 7 or 8 or 10)

14. treatment outcome/ or clinical outcome/ or outcome assessment/

15. "cost"/

16. (cost\*1 or economics).tw,kw,dq,hw.

17. (pc or ae).fs.

18. adverse drug reaction/ or drug eruption/ or drug hypersensitivity/

19. mortality/ or hospital mortality/ or infant mortality/

20. exp evaluation study/

21. (3 or 11 or 12) and (2 or 14 or 15 or 16 or 17 or 18 or 19 or 20)

22. 13 or 21

23. developing country/

24. (austere or (limited adj2 resource\*) or (low adj2 resource\*) or (transitioning adj econom\*) or (third adj world) or LMIC or LMICs or (lami adj countr\*) or (transitional adj countr\*) or (low adj gdp) or (low adj gnp) or (low adj gross adj domestic) or (low adj gross adj national) or ((emerging or developing or (low adj income) or (middle adj income) or (low adj3 middle) or underdeveloped or under-developed or (less\* adj developed) or underserved or under-served or deprived or poor\*) and (countr\* or nation\*1 or econom\* or population or world))).tw,kw.

25. exp Africa/

26. exp "south and central america"/ or mexico/

27. asia/ or far east/ or china/ or exp korea/ or mongolia/ or philippines/ or kazakhstan/ or kyrgyzstan/ or tajikistan/ or turkmenistan/ or uzbekistan/ or middle east/ or iran/ or iraq/ or jordan/ or lebanon/ or oman/ or palestine/ or saudi arabia/ or syrian arab republic/ or "turkey (republic)"/ or yemen/ or southeast asia/ or borneo/ or cambodia/ or indonesia/ or laos/ or malaysia/ or myanmar/ or papua new guinea/ or thailand/ or timor-leste/ or viet nam/ or exp south asia/

28. exp "arctic and antarctic"/

29. atlantic islands/ or bermuda/ or bouvet island/ or exp caribbean islands/ or "falkland islands (malvinas)"/ or saint helena/ or "saint pierre and miquelon"/ or "sao tome and principe"/ or "south georgia and the south sandwich islands"/ or exp indian ocean/ or exp pacific ocean/

30. (Afghanistan or Albania or Algeria or Angola or Antigua or Argentina or Armenia\* or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Barbuda or Belarus or Byelarus\* or Byelorussian or Belorussian or Belorus\* or Belize or Benin or Bhutan or Bolivia or Bosnia or Botswana or Brasil or Brazil or Bulgaria or (Burkina adj Fas\*) or (Upper adj Volta) or Burma or Burundi or Cambodia or Khmer or Kampuchea or Cameron\* or Cameroon\* or (Cape adj Verde) or (Cabo adj Verde) or (Central adj African adj Republic) or Chad or Chile or China or Colombia or Comoros or (Comoro adj Island\*) or Comores or Mayotte or Congo or Kongo or (Cook adj Island\*) or (Costa adj Rica) or (Cote adj D'ivoire) or Croatia or Cuba or Cyprus or (Czech adj Republic) or Czechoslovakia or Djibouti or Dominica or Dominican or (East adj Timor) or (East adj Timur) or Ecuador or Egypt or El-Salvador or (Equatorial adj Guinea) or Eritrea or Estonia or Ethiopia or Fiji or (French adj Somaliland) or Futuna or Gabon or (Gabonese adj Republic) or Gambia or Gaza or (Georgia\* adj Republic) or Ghana or Grenada or Guam or Guatemala or Guinea or Guiana or Guyana or Haiti or Herzeg\* or Hercegovina or Honduras or Hungary or India or Indonesia or Iran or Iraq or (Ivory adj Coast) or Jamaica or Jordan or Kazakh\* or Kenya or Kiribati or Korea or Kosovo or (Kyrgyz adj Republic) or Kyrgyzstan or Kirghizia or Kirghiz or Kirgizstan or Laos or (Lao\* adj2 Democratic adj Republic) or (Lao\* adj PDR) or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or (Magalasy adj Republic) or Malawi or Malay\* or Sabah or Sarawak or Maldives or Mali or (Marshall adj Island\*) or Mauritania or Mauritius or (Agalega adj Island\*) or Mexico or Micronesia or Moldov\* or Mongolia or Montserrat or Montenegro or Morocco or Ifni or Mozambique or Myanma\* or Namibia or Nauru or Nepal or (Netherlands adj Antilles) or (Dutch adj Antilles) or (New adj Guinea) or (New adj Caledonia) or Nicaragua or Niue or Niger or Nigeria or (Northern adj Mariana adj Island\*) or Nyasaland or Oman or Pakistan or Palau or Panama or (Papua adj New adj Guinea) or PNG or Palestine or Paraguay or Peru or Philipines or Philippines or Phillipines or Phillippines or Poland or (Puerto adj Rico) or Yemen or Romania or Roumania or Rumania or Russia\* or Rwanda or Ruanda or (Saint adj Kitts) or (St adj Kitts) or Nevis or (Saint adj Vincent) or (St adj Vincent) or Grenadines or Samoa\* or (Navigator adj Island\*) or (Saint adj Lucia) or (St adj Lucia) or (Saint adj Helena) or (St adj Helena) or (Sao adj Tome) or (Saudi adj Arabia) or Senegal or Serbia or Seychelles or (Sierra adj Leone) or Slovenia or Slovak\* or (South adj Africa) or (Solomon adj Island\*) or Somalia or (Sri adj Lanka) or Ceylon or Sudan or Surinam\* or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Tibet or Timor-Leste or Togo or (Togolese adj Republic) or Tokelau or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Tuvalu or Uganda or Ukraine or Uruguay or Urundi or USSR or (Soviet adj Union) or "Union of Soviet Socialist Republics" or Uzbekistan or Vanuatu or (New adj Hebrides) or Venezuela or Vietnam or (Viet adj Nam) or (Wallis adj Futuna) or (United adj Arab adj Republic) or (West adj Bank) or (West adj Indies) or Yemen or Yugoslavia or Zaire or Zambia or Zimbabwe or Rhodesia).tw,kw.

31. (africa or americas or caribbean or (central adj America) or (latin adj America) or (south adj America) or (eastern adj Europe) or Transcaucasia or antarctic or (atlantic adj island\*) or (indian adj ocean adj island\*) or (pacific adj island\*) or polynesia or (central adj asia) or (southeast\* adj asia) or (south-east\* adj asia) or borneo or mekong or (western adj asia) or (middle adj east) or (far adj east)).tw,kw.

32. europe/ or exp eastern europe/

33. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34. 22 and 33

35. (newborn\* or new-born\* or baby or babies or neonat\* or neo-nat\* or infan\* or toddler\* or pre-schooler\* or preschooler\* or kinder or kinders or kindergarten\* or kinder-aged or boy or boys or girl or girls or child or children or childhood or pediatric\* or paediatric\* or adolescen\* or youth or youths or teen or teens or teenage\* or school-age\* or schoolage\* or school-child\* or schoolchild\* or school-girl\* or schoolgirl\* or school-boy\* or schoolboy\*).af.

36. 34 and 35

37. \*antimicrobial stewardship/ and 33

38. 36 or 37

39. limit 38 to (conference abstract or "conference review" or editorial or letter)

40. 38 not 39

**Database:**

**PUBMED**

Search 1

(antimicrobial-stewardship OR anti-microbial-stewardship) AND (treatment-outcome OR costs OR cost OR economics OR adverse-effect\* OR adverse-event\* OR side-effect\* OR drug-hypersensitiv\* OR drug-hyper-sensitiv\* OR drug-eruption OR mortalit\* OR fatal-outcome OR evaluation) AND (newborn\* OR new-born\* OR baby OR babies OR neonat\* OR neo-nat\* OR infan\* OR toddler\* OR pre-schooler\* OR preschooler\* OR kinder OR kinders OR kindergarten\* OR kinder-aged OR boy OR boys OR girl OR girls OR child OR children OR childhood OR pediatric\* OR paediatric\* OR adolescen\* OR youth OR youths OR teen OR teens OR teenage\* OR school-age\* OR schoolage\* OR school-child\* OR schoolchild\* OR school-girl\* OR schoolgirl\* OR school-boy\* OR schoolboy\*) AND (NOTNLM OR publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR indatareview[sb] OR pubstatusaheadofprint) AND (*LMIC filter)*

Pubmed search 2

(antibacterial OR anti-bacterial OR antibiotic\* OR antimicrob\* OR anti-microb\*) AND (over-prescrib\* OR over-prescription OR misuse\* OR drug-utilisation-review OR drug-utilization-review OR practice-pattern OR guideline-adherence OR inappropriate-prescribing) AND (treatment-outcome OR costs OR cost OR economics OR adverse-effect\* OR adverse-event\* OR side-effect\* OR drug-hypersensitiv\* OR drug-hyper-sensitiv\* OR drug-eruption OR mortalit\* OR fatal-outcome OR evaluation) AND (newborn\* OR new-born\* OR baby OR babies OR neonat\* OR neo-nat\* OR infan\* OR toddler\* OR pre-schooler\* OR preschooler\* OR kinder OR kinders OR kindergarten\* OR kinder-aged OR boy OR boys OR girl OR girls OR child OR children OR childhood OR pediatric\* OR paediatric\* OR adolescen\* OR youth OR youths OR teen OR teens OR teenage\* OR school-age\* OR schoolage\* OR school-child\* OR schoolchild\* OR school-girl\* OR schoolgirl\* OR school-boy\* OR schoolboy\*) AND (NOTNLM OR publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR indatareview[sb] OR pubstatusaheadofprint) AND (*LMIC filter)*

**LMIC Pubmed Filter**

(austere OR limited resource\* OR "resource limited" OR low resource\* OR transitioning econom\* OR lami countr\* OR transitional countr\* OR "low gdp" OR "low gnp" OR "low gross domestic" OR "low gross national" OR ((emerging OR developing OR "low income" OR "middle income" OR (low AND middle) OR underdeveloped OR "under developed" OR under-developed OR underserved OR "under served" OR under-served OR (less\* AND developed) OR derived OR poor) AND (countr\* OR nation\* OR econom\* OR population OR world)) OR "third world" OR lmic OR lmics) OR afghanistan OR albania OR algeria OR angola OR antigua OR argentina OR Armenia\* OR aruba OR azerbaijan OR bahrain OR bangladesh OR barbados OR barbuda OR belarus OR Byelarus\* OR byelorussian OR Belorus\* OR belize OR benin OR bhutan OR bolivia OR bosnia OR botswana OR brasil OR brazil OR bulgaria OR burkina Fas\* OR "Upper Volta" OR burma OR burundi OR cambodia OR khmer OR kampuchea OR Cameron\* OR Cameroon\* OR "Cape Verde" OR "Cabo Verde" OR "Central African Republic" OR chad OR chile OR china OR colombia OR comoros OR comoro Island\* OR comores OR mayotte OR congo OR kongo OR cook Island\* OR "Costa Rica" OR "Cote D'ivoire" OR croatia OR cuba OR cyprus OR "Czech Republic" OR czechoslovakia OR djibouti OR dominica OR dominican OR "East Timor" OR "East Timur" OR ecuador OR egypt OR el-salvador OR "Equatorial Guinea" OR eritrea OR estonia OR ethiopia OR fiji OR "French Somaliland" OR futuna OR gabon OR "Gabonese Republic" OR gambia OR gaza OR (Georgia\* AND republic) OR ghana OR grenada OR guam OR guatemala OR guinea OR guiana OR guyana OR haiti OR Herzeg\* OR hercegovina OR honduras OR hungary OR india OR indonesia OR iran OR iraq OR "Ivory Coast" OR jamaica OR jordan OR Kazakh\* OR kenya OR kiribati OR korea OR kosovo OR "Kyrgyz Republic" OR kyrgyzstan OR kirghizia OR kirghiz OR kyrgyzstan OR Lao OR laos OR latvia OR lebanon OR lesotho OR basutoland OR liberia OR libya OR lithuania OR macedonia OR madagascar OR "Magalasy Republic" OR malawi OR Malay\* OR sabah OR sarawak OR maldives OR mali OR marshall Island\* OR mauritania OR mauritius OR galega Island\* OR mexico OR micronesia OR Moldov\* OR mongolia OR montserrat OR montenegro OR morocco OR ifni OR mozambique OR Myanma\* OR namibia OR nauru OR nepal OR "Netherlands Antilles" OR "Dutch Antilles" OR "New Guinea" OR "New Caledonia" OR nicaragua OR niue OR niger OR nigeria OR ("Northern Mariana" AND Island\*) OR nyasaland OR oman OR pakistan OR palau OR panama OR "Papua New Guinea" OR PNG OR palestine OR paraguay OR peru OR philippines OR philippines OR philippines OR philippines OR poland OR "Puerto Rico" OR yemen OR romania OR roumania OR rumania OR Russia\* OR rwanda OR ruanda OR "Saint Kitts" OR "St Kitts" OR nevis OR "Saint Vincent" OR "St Vincent" OR grenadines OR Samoa\* OR navigator Island\* OR "Saint Lucia" OR "St Lucia" OR "Saint Helena" OR "St Helena" OR "Sao Tome" OR "Saudi Arabia" OR senegal OR serbia OR seychelles OR "Sierra Leone" OR slovenia OR Slovak\* OR "South Africa" OR solomon Island\* OR somalia OR "Sri Lanka" OR ceylon OR sudan OR Surinam\* OR swaziland OR syria OR tajikistan OR tadzhikistan OR tadjikistan OR tadzhik OR tanzania OR thailand OR tibet OR timor-leste OR togo OR "Togolese Republic" OR tokelau OR tonga OR trinidad OR tobago OR tunisia OR turkey OR turkmenistan OR turkmen OR tuvalu OR uganda OR ukraine OR uruguay OR urundi OR ussr OR "Soviet Union" OR "Union of Soviet Socialist Republics" OR uzbekistan OR vanuatu OR "New Hebrides" OR venezuela OR vietnam OR "Viet Nam" OR "Wallis Futuna" OR "United Arab Republic" OR "West Bank" OR "West Indies" OR yemen OR yugoslavia OR zaire OR zambia OR zimbabwe OR rhodesia OR africa OR americas OR caribbean OR "central America" OR "latin America" OR "south America" OR "eastern Europe" OR transcaucasia OR antarctic OR atlantic island\* OR "indian ocean" OR pacific island\* OR polynesia OR "central asia" OR (southeast\* AND asia) OR (south-east\* AND asia) OR "south east asia" OR "south eastern asia" OR borneo OR mekong OR "western asia" OR "middle east" OR "far east"

**Supplemental Digital Content 2.** PRISMA table of included studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **Country or region** | **Study design** | | | **Study sizeand setting** | | | **Population** | | | **Intervention** | | | **Comparison** | | **Outcomes** | | | **Risk of bias** |
| **Implementation of AMS bundle** | | | | | | | | | | | | | | | | | | | |
| Ding H, 200814 | China | | Uncontrolled before and after | | | Paediatric intensive care unit Beijing Children’s hospital | | | Prescribers of first 15 clinical records of every month each year during study period | | | 1 Jan 2005 to 31 Dec 2006  (1) educating the pediatricians on antibiotic prescribing, (2) applying an antimicrobial spectrum chart, and (3) controlling the prescription of specific antibiotics with the use of a guideline. | | Pre-intervention period: 1 Jan 2002 to 31 Dec 2004 | | | | 1. antibiotic cost/patient/day  2. choice of antibiotic  3. indication  4. resistance rates  5. Cost | MEDIUM |
| Lu C, 201817 | China | | Uncontrolled interrupted time series | | | NICU  Pre-intervention n = 7,754  Post-intervention n = 5786  No sig difference in baseline characteristics | | | All prescribers in NICU | | | audit, feedback, prior authorization, and point-of-prescription interventions (automatic 48hr stop for empiric prescriptions)  June 1, 2016, to May 31, 2017 | | Pre-intervention January 1, 2015, to May 31, 2016 | | | | 1. change in total antibiotic days per 1,000 patient-days.  Secondary:  A) readmissions for infection, B) late-onset sepsis  C) length of stay D) necrotizing enterocolitis  E) death in infants ≤32/40  F) prevalence of MDRO colonization | MEDIUM |
| Wei X, 201719 | Guangxi, China | | Controlled before-after | | | One county hospital  Population 810, 000  N =3767 (2011) N=4452 (2014) | | | Prescribers to children 2–14 years of age presenting in outpatients with a primary diagnosis of upper respiratory tract infection (URTI) | | | Policy implementation plus AMS program: National essential medicines scheme and zero-mark up policy in addition to ASP with AMS leadership committee, training, peer review of prescriptions and restrictions for overprescribing | | Control county hospital  Population 440,000  N = 1809 in 2011/2333 in 2014 | | | | 1. Outpatient antibiotic prescribing rate (APR) 2. Broad spectrum APR 3. Reduction in IV APR 4. Reduction in cost   Inpatient population: inappropriate abx prescribing | HIGH |
| Wei X, 201920  (*f/up of Wei X, Zhang Z, 2017)21* | China  Guangxi province | | Follow up of cluster randomized controlled trial | | | Rong county (14 facilities and 1:1 cluster randomization ratio) | | | As above | | | As above  Also conducted 15 in-depth interviews to understand how interventions were sustained | | As above | | | | APR assessed 12 months after the trial ended (18 month follow up period) | MEDIUM |
| Wei X, Zhang Z, 201721 | China  Guangxi province | | Cluster randomized controlled trial | | | 25 primary care township hospital outpatients | | | Prescribers to 2-14 yr olds given prescription for primary diagnosis URTI | | | evidence-based prescribing guideline, training and monthly prescribing peer-review meetings for doctors, and brief education for caregivers during consultations and an educational waiting room video for caregiver  6-month f/up period | | Usual care - prescription at doctors discretion at control facilities | | | | 1. APR – cluster level proportion of antibiotic prescription for URTI in final 3 months of 6-month intervention period  Secondary:  A) more than one antibiotic B) any broad-spectrum antibiotic(s), and C) any intravenously administered antibiotic(s).  D) the full prescription cost (including the total of any consultation costs) | LOW |
| Zhang Z, 2018  *25* | China Guangxi province | | | Cost-effectiveness of Wei X, Zhang Z, 201721 | | | See above | | | See above | | | measuring costs of consultation (time cost of doctor), prescription monitoring process and peer-review meetings (time cost of participants) and medication costs. | |  | | *Cost-effectiveness of above intervention*  Incremental cost-effectiveness ratios (dividing the mean difference in cost of the two trial arms by the mean difference in APR) | | N/A |
| Zhang, Chen, Chen, 201826 | China  Shandong Province | | Uncontrolled before and after | | | Pediatric Center, inpatient  Pre intervention: n= 21,854  Post intervention n= 29,389 | | | Prescribers to all pediatric wards and NICU | | | ASP team, review prescriptions, real-time feedback, ‘real-time’ antibiotic resistance reporting, rounds, education on antibiotics standard use, antibiotic prescription ‘privileges’, monthly multi-disciplinary antibiotic rounds, inappropriate antibiotic use reporting to hospital leaders, department leaders and nursing staff monthly  April 2011 to March 2014 | | Pre-intervention  April 2009 to March 2011 | | | | 1. consumption of antibiotics 2. defined daily dose (DDD)  3. isolation of multidrug-resistant organisms (MDRO) and resistance rate of antibiotics | HIGH |
| Zou W, 201528 | China | | Uncontrolled before and after | | | Dept of Pediatric Surgery, tertiary care, teaching university-based hospital  N= 234 | | | Prescribers to all inpatients with intussusception after successful air enema reduction | | | Chinese national policy implementation; standardized prescriptions; ‘expert team’; antibiotic management guidelines | | Pre- and post- implementation  Phase I January 1, 2011 to October 31, 2011  Phase II November 1, 2011 to December 31, 2013 | | | | 1. Antibiotic use, indication, type | MEDIUM |
| Murni I, 201529 | Indonesia | | Uncontrolled before and after | | | PICU and pediatric wards  N=1227 vs 1419 (pre vs. post) | | | All prescribers and healthcare workers (infection control) | | | educational seminars, teaching module, reminders/checklists, audit and performance feedback,  infection control  f/up period 12 months | | Pre-intervention  12 months | | | | 1. proportion of patients with an HAI.  Secondary:  A) proportion patients exposed to inappropriate antibiotic use B) HCW hand-hygiene compliance   1. C) mortality rate | medium |
| Ruvinsky, 201430 | Argentina | | Uncontrolled before and after | | | Tertiary care teaching hospital  N=376 (pre-intervention) vs. 357 (post) | | | Prescribers to patients in ED, ICU and wards 1m-16 yrs  (Medical assistants, fellow residents, pharmacists and infectious disease specialists) | | | Hospital guidelines, twenty workshops conducted including interactive case discussion, dissemination of Mx algorithms  (IV antibiotic prescriptions randomly selected from pharmacy database excluding burn patients and prophylaxis) | | Pre- and post- implementation  From July 1st, 2010 to June 30th, 2011. The pre-intervention period, the intervention and the post-intervention period lasted 4 months each | | | | 1. 1. Adequacy of antibiotic prescription according to hospital guidelines including dose, interval and duration | HIGH |
| Chowdhury, 201831 | Bangladesh | | Uncontrolled Before and after | | | Outpatient management of pediatric and adult ARI in Dhaka city. | | | Drug sellers and pharmacists in Dhaka city. | | | One day educational program on the differentiation of simple from complicated ARI and appropriate use of antibiotics. Provision of a guideline and poster as a reminder. | | Survey of prescribing practice through presentation of “fake patients” with complaint of ARI. | | | | 1. Rates of antibiotic prescriptions.  2. Proportion of patients referred.  3. Rates of symptomatic prescriptions (antihistamines, bronchodilators, syrup).   1. 4. Quality of advice given. | MEDIUM |
| Sultana, 201732 | Bangladesh | | Uncontrolled before-after | | | Inpatient.  Bangabandhu Sheikh Mujib Medical University. | | | Prescribers to all inpatients departments of Obstetrics, Paediatrics & Internal Medicine. | | | Development of guideline using local microbiology data.  Guideline available online.  SMS reminders to prescribers.  Education package for prescribers. | | Prescribing practices were audited from each department from immediately before and 15 days after implementation of the intervention. | | | | 1. Proportion of admissions receiving antibiotic.  2. DDD/100 patient bed days.  3. DDD consumed per admitted patient.  4. Coverage of guideline.  5.Adherence to guideline | HIGH |
| Calil, 200137 | Brazil | | Uncontrolled before and after | | | 1 neonatal care unit university hospital | | | All prescribers and healthcare workers | | | (1) appropriate training of the whole health care team on infection control, and the rational usage of antibiotics and (2) suppression of usage of third-generation cephalosporins. | | Pre-intervention  1 year of data in each period: before, during and 4 years after intervention | | | | 1. occurrence of nosocomial infections caused by multi-resistant bacteria | MEDIUM |
| Gonzalez Ochoa, 199638 | Cuba | | Cluster randomized controlled trial | | | 40 primary healthcare clinics  population covered served by these clinics = 1600 | | | Prescribers to children < 5 yrs old presenting with acute respiratory infection | | | Education to family physicians in areas A and B  Education to families in areas A and C  Clinical and therapeutic guidelines on ARI in children  Physician education: a) 1x 3-hour session with a test of physicians’ ARI knowledge, followed by a  video on clinical exploration of the childhood respiratory tract and discussion; (b) an audio-visual slide presentation on treatment of ARI in children and discussion; c) discussion of clinical and therapeutic guidelines  - monthly visits by research team to provide advisory assistance and further education  - 6 month follow up session  Community education: a) group discussions in participants’ homes (20 discussions, 9 participants in each); b) waiting room education sessions; c) distribution of educational materials by health team personnel; d) printed material disseminated by health brigade members | | Area D – control group with routine care. | | | | 1. Number of antibiotic (over) prescriptions for mild ARI episodes | HIGH |
| Opondo C, 201141 | Kenya | | Cluster randomized controlled trial | | | 8 district hospitals N=1160 | | | Prescribers to children 2-59 months with acute non-bloody diarrhea | | | Training health workers on the use of evidence-based guidelines for acute non-bloody diarrhea, supervision, local facilitator to promote guideline implementation over 18 months, 6-monthly surveys, written and face to face feedback to prescribers | | Partial intervention in control hospitals (shorter didactic training, clinical practice guidelines and job aids, written feedback on interval surveys) | | | | 1. Absolute risk  reduction for  receiving antibiotic  for inappropriate   1. indication | HIGH |
| Haque 201744 | Pakistan | | Uncontrolled before and after study | | | Cardio-thoracic PICU | | | All prescribers and healthcare workers and pharmacist | | | pharmacist-led prospective-audit-with-feedback ASP from April to June 2016  Implemented during each ward round | | Pre intervention | | | | 1. Days of therapy /1000 patient days 2. Mortality 3. Antibiotic utilization 4. Appropriate use of antibiotic for the treatment of culture negative like symptoms   Cost | LOW |
| Kalaba, 201846 | Serbia | | Uncontrolled before and after | | | 125 bed tertiary care hospital | | | All prescribers in pediatric tertiary care hospital | | | drug and therapeutics committee; antibiotic prescribing policies, guidelines and hospital formularies; biannual analysis of resistance patterns among the isolates from the central ICU and its distribution to all clinicians; preauthorization of reserve antibiotics by clinical pharmacology specialist; consulting clinical pharmacologists and infectious diseases specialists when prescribing antibiotics to complex patients. | | Antibiotic restriction only | | | | 1. Combined antimicrobial utilization data with cumulative resistance in 2010 versus 2014  2. Cost per DDD | HIGH |
| **Guideline or policy implementation (national government or local)** | | | | | | | | | | | | | | | | | | | |
| Liang, 201416 | Shenzhen, China | | Controlled before-after | | | Community Health Centres (CHC)  n = 14189  5 (intervention) vs. 2 CHC | | | Prescribers to children <5 yrs presenting with acute upper respiratory tract infection (AURTI) | | | Change in governance structure from affiliated to independent to eliminate physicians’ financial incentive to prescribe medicines.  Dec 2010 Government essential medicine policy included a list of essential medications, a zero mark-up policy and changes in procurement | | 2 control CHCs in a separate subdistrict  n = 9292 | | | | 1. % reduction/month in proportion of patients receiving injectable antibiotics, 2 or more antibiotics, 2. change in type of antibiotics prescribed 3. reduction in cost   (12 m f/up) | HIGH |
| Zhang, Chen, Chen 200824 | China | | Uncontrolled before and after  Antibiotic data collected from central computer database for entire year | | | **Inpatients**  5 hospitals  Beijing  Shanghai  Chongqing  Guangzhou | | | Inpatients of all wards (multiple medical and surgical specialties) | | | October 2004, the Ministry of Health of P.R. China issued the Guidelines for Antibacterial Use in Clinical Practice including attendance at yearly lectures and prescribing restrictions | | Pre-intervention period 2002-2003 | | | | 1. Defined Daily Doses (DDD)/100 bed days 2. Type of antibiotics used | HIGH |
| Zhang, Fan, Yang, 200827 | China | | Uncontrolled before and after | | | **Outpatient** clinics 5 hospitals  Beijing  Shanghai  Chongqing  Guangzhou | | | Prescribers to children attending outpatient clinic, outpatient visits ranged from 1398 to 5375 visits per day. | | | October 2004, the Ministry of Health of P.R. China issued the Guidelines for Antibacterial Use in Clinical Practice including attendance at twice yearly lectures and prescribing restrictions | | Pre-intervention  2002-2003 | | | | Defined Daily Doses and Drug Utilization 90% | HIGH |
| Jinka D, 201733 | India | | Uncontrolled interrupted time series | | | Neonatal intensive care unit  Pre: n=1176  Post: n=1279 | | | Prescribers in a rural hospital, 30 bed NICU in-born and out-born | | | Antibiotic policy for neonatal sepsis Jan 1st 2014 | | One year before intervention | | | | 1. Antibiotic consumption DDD/100 patient-days one year after intervention   Secondary:  A) proportion of admitted newborns on any antibiotics B) choice of antibiotic C) overall mortality D) sepsis-related mortality | MEDIUM |
| Murki, 200934 | India | | Uncontrolled before and after | | | NICU of tertiary hospital. | | | All prescribers. | | | Restriction in Cephalosporins. | | 1 year of data pre and post restriction. | | | | 1. Rates of any antibiotics and individual rates of cephalosporin, aminoglycosides, ampicillin, ciproflocaxin, pip-taz and meropenem.   1. 2. Rates of ESBL and proportion of Gram-negative bacteria resistant to individual antibiotics. | HIGH |
| Lee, 200742 | Korea | | Uncontrolled before and after | | | 1 university children's hospital  300 bed, includes NICU, PICU, oncology | | | All prescribers | | | Change in antibiotic policy through change in hospital formulary: the use of extended-spectrum cephalosporins was discouraged if possible, and instead, prescriptions of b-lactam/b-lactamase inhibitor combinations were encouraged. | | Pre-intervention  1 year of data in each period: before, during and after intervention | | | | 1. reduce extended spectrum cephalosporin use  2. prevalence of ESBL *K. pneumoniae* and *E coli* from sterile sites  3. change in the clinical outcome of invasive diseases caused by *E. coli or K. pneumoniae,* | medium |
| Berild, 200845 | Russia | | Controlled before-after | | | Pediatric infection hospital, 200 beds  Approx. 6500 admissions per year | | | Prescribers to 1 month to 14 year-old with RTI and  1 – 14 years with gastrointestinal infection | | | Diagnosis and treatment guidelines (based on local resistance data and consensus) given to physicians in one of the 2 gastroenterology and respiratory wards | | 2 control wards (one of the 2 gastroenterology and respiratory) | | | | 1. APR   Secondary:  A) mortality  B) duration of fever  C) duration of hospital stay  D) cost | HIGH |
| **Clinical decision tool** | | | | | | | | | | | | | | | | | | | |
| Wu, 201722 | China | | | Uncontrolled before and after | | | All ward inpatients tertiary hospital  N=366 | | | Prescribers to children <14 y with community acquired LRTI | | | Procalcitonin algorithm  January 1, 2015 and July 31, 2016 at presentation and repeated during admission  N = 183 | | standard guidelines January 1, 2010 and December 31, 2011  n = 183 | | 1. reduction of the duration of antibiotic treatment  2. A/E from abx  3. Length of hospital stay | | MEDIUM |
| Torres, 201429 | Argentina | | | Randomized controlled trial | | | outpatient clinic of a pediatric hospital between April 2010 and March 2011  N=120 | | | Prescribers to children 3 – 60 months with WHO non-severe pneumonia | | | Bacterial pneumonia score which includes white blood cell count, fever, age, CXR score | | Standard care | | 1. Proportion of patients receiving abx initially  Secondary  1. clinical outcome to day 10 | | MEDIUM |
| Keitel, 201735 | Tanzania | | | Randomized controlled trial | | | 9 Outpatient clinics  N=1586 intervention arm vs. 1583 control arm | | | Healthcare workers of children 2-59 months with acute febrile illness | | | Electronic algorithm e-POCT: treatment based on a few clinical signs and POCT results (Malaria rapid diagnostic test, Hb and oximeter for all; CRP, PCT, glucometer for selected patients) | | Electronic algorithm ALMANACH | | 1. Clinical outcome by day 7 f/up  Secondary  A) Proportion of antibiotic prescription on day 0 and between day 1 and day 6,  B) primary referrals  C) severe adverse events by day 30 (secondary hospitalizations and deaths) | | LOW |
| Shao, 201536 | Tanzania – rural and urban settings | | | Controlled non-inferiority trial | | | 4 primary healthcare facilities  N=1467  (844 vs. 633) | | | Healthcare workers of 2m to 5y olds presenting to the primary healthcare facility | | | Implementation of the Algorithm for the MANAgement of Childhood illness (ALMANACH) | | Routine practice (Integrated Management of Childhood Illness algorithm) | | 1. proportion of children cured at day 7 and who received antibiotics on day 0 | | LOW |
| Bucher, 201243 | Peru | | | Randomized controlled trial | | | 1x pediatric ED  N=201 | | | Prescribers to <5yr olds with diarrhea <5 day duration, with or without vomiting or fever | | | Antibiotic initiation guided by fecal rotavirus rapid test in combination with a fecal leukocyte test | | fecal leukocyte test only. | | 1. RR of receiving antibiotics | | HIGH |
| Ozkaya, 200947 | Turkey | | | Non-randomized controlled trial | | | Pediatric emergency department  N=97 | | | Prescribers to 3-14 yr olds with mild influenza-like illness | | | Antibiotic initiation guided by influenza rapid test | | No investigation | | 1. RR of receiving antibiotics | | HIGH |
| Do NT, 201648 | Northern Vietnam | | | Randomized controlled trial (open label) | | | 10x Primary healthcare clinic N=1028 | | | Prescribers to children 1-15y with non-severe acute respiratory tract infection | | | Point-of-care C-reactive protein (CRP) | | Routine care | | 1. Number of patients receiving any antibiotic within 14 days  Secondary:  abx activity in urine (D3, 4, 5), immediate abx prescription, subsequent abx use, prescription on second visit, source of abx not prescribed at enrolment, frequency of reconsultation, hospital admission or death, time to resolution of symptoms | | LOW |
| **Financial disincentive** | | | | | | | | | | | | | | | | | | | |
| Gong, 201615 | Guangzhou, China | | | Uncontrolled interrupted time series | | | Inpatient and outpatient, 1012-bed pediatric hospital  n = 29,363,808 | | | All prescribers | | | ‘Financially punished’ audit and feedback Oct 2011 to Nov 2012  - automatic reports of patients receiving antibiotics and review of appropriateness and feedback to prescriber | | 1. Pre-intervention Jan – April 2011  2. Formulary restriction and prior authorization alone May to Sep 2011 | | 1. Monthly average use of abx  2. Expenditure on abx relative to all other medications | | MEDIUM |
| Xu, 201923 | **China** | | | Uncontrolled before and after | | | Outpatient, inpatient and ED of Children’s Hospital  N = 5 226 278 outpatients  N = 2 421 836 emergency patients,  N = 24 296 inpatients | | | All prescribers | | | 2011 – 2014: implementation of Ministry of Health antibiotic policy (restricted antibiotics, rewards and ‘punishment’ and expert consult)  2014 - 2017, awards and ‘punishments’ will be further increased, special comments on the use of special use antibacterial drugs will be carried out | | pre-management (2010-2011), post-management first phase (2012-2013), post-management second phase (2014-2015) and post-management third phase (2016-2017)  yearly outcome assessment, 2 interventions across 7 year period | | 1. Antibiotic usage  2. MDR-GNB detection rate | | MEDIUM |
| **Audit and feedback of restricted antibiotics** | | | | | | | | | | | | | | | | | | | |
| Rahbarimanesh, 201940 | Iran | | | Uncontrolled before and after | | | One children’s hospital.  N=68 (pre) N = 67 (post) | | | Prescribers to inpatients on vancomycin or meropenem excluding low birth weight, hospital admission <1 week, congenital anomaly, surgical patients, or transfers. | | | Audit and feedback by ASP team on meropenem and vancomycin use over 12 months  2015-2016 | | Pre-intervention – 12 months | | 1. Appropriate use of vancomycin and meropenem 2. mortality rate  3. antibiotic prescription  4. antibiotic dose  5. antibiotic duration  6. length of hospital stay  7. positive blood cultures | | HIGH |
| **Cost effectiveness** | | | | | | | | | | | | | | | | | | | |
| Zhang Z, 2018  (*Cost-effectiveness of study )25* Wei X, Zhang Z, 201721 | China **Guangxi province** | | | See 11 | | | See 11 | | | See 11 | | | measuring costs of consultation (time cost of doctor), prescription monitoring process and peer-review meetings (time cost of participants) and medication costs. | |  | | *Cost-effectiveness of above intervention*  Incremental cost-effectiveness ratios (dividing the mean difference in cost of the two trial arms by the mean difference in APR) | | N/A |

Supplemental Digital Content 3. PRISMA table of outcomes of individual studies included in systematic review

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study, year** | | **Outcome measurement** | | **Findings vs. control or prior to intervention (selected)** | **Summary** | |
| **Implementation of AMS bundle** | | | | | | |
| Ding H, 200814 | 1. antibiotic cost/patient/day 2. indication 3. choice of antibiotic 4. resistance rates | | 1. USD 17.3 (pre) vs. 12.7 (post) cost/patient-day; p<0.05 (25% reduction)  Duration 6 vs. 5.1 days; p=NS  Rate 98.7% vs. 93.5% p=NS  2. Empiric 83.4% (pre) vs. 66.6% (post); p<0.01  3. penicillin 4% vs. 3% p=NS; BL/BLI 4 vs. 44% p=<0.01; 2GC 13 vs. 47.9% p<0.01; 3GC 52.9 vs. 17.2% p<0.01; macrolides 20 vs. 11.5% p<0.01, no change in carbapenem use.  4. (colonization or infection) Imipenem resistant PsA 21.7 vs. 9.9% p<0.05; cefepime resistant PsA 22.5 vs. 10.6% p<0.05, ceftazidime resistant PsA 14.6 vs. 7.5% p<0.05; cefepime resistant E. coli 61.5 vs. 42.7% p<0.01; cefepime resistant kleb pneumo 66.4 vs. 34% p>0.01 | | The average duration and rate of antibiotic use did not significantly decrease after the intervention  Significant reduction in empiric treatment  Reduced prescription of 3GC  Increase in use of 2GC and BL-BLI  Reduction in incidence of bacterial resistance rates |
| Lu C, 201917 | 1. change in total antibiotic days per 1,000 patient-days.  Secondary:  A) readmissions for infection,  B) late-onset sepsis  C) length of stay (LOS) D) necrotizing enterocolitis (NEC)  E) death in infants ≤32/40  F) prevalence of MDRO colonization | | 543.2 (pre) vs. 380.2 (post) DOT/1,000 patient- days. No change in rate of use of selected antibiotics. Rule out sepsis 250 (47) vs. 130 (36) p=0.001  Readmission rate: 1.2% vs. 1.1%; p = 0.16  LOS: 11.4% vs. 6.5%; p = 0.01  Composite difference in LOS, NEC or death: 17.2%; 95% CI, 8.6–25.8 vs.15.8%; 95% CI, 9.0–22.6  MDRO colonization: 1.4% vs. 1.0%; p = 0.02 | | 30% reduction in antibiotic days of treatment, increased targeted antibiotic use, reduction in length of stay and MDRO colonization rate. No change in readmission rate or mortality. |
| Wei X, 201719 | 1. Outpatient antibiotic prescribing rate (APR) 2. Broad spectrum APR 3. Reduction in IV APR 4. Reduction in cost 5. Inpatient APR | | 1. APR has reduced in the intervention group vs. comparison (-21%, 95% CI: -23%, -18%, p<0.001).  2. Broad spectrum antibiotic prescription reduced from 95% to 81% in intervention group but remained the same 89% vs. 88% in comparison group; difference -10 CI – 15, -16, p<0.001  3. Decrease in intravenous antibiotics in the intervention vs. the comparison group (-58%, 95% CI: -64%, -52%, p <0.001).  4. Average costs per prescription with antibiotics reduced 31 USD in the intervention vs. the comparison group (-31, 95% CI: -35, -28, , p<0.001), and decreased 75% in the intervention group (p<0.01).  5. No significant reduction in inpatient inappropriate APR (51% to 42% pre and post intervention) | | AMS program paired with national policy implementation resulted in significant reduction in outpatient APR in pre and post-intervention periods in intervention hospitals, and compared to control CHC. There was a non-significant reduction in inappropriate prescriptions for inpatients.  There was marked difference in baseline antibiotic prescribing rate for control CHCs |
| Wei X, 201920  (*f/up of Wei X, Zhang Z, 2017)* | APR assessed 12 months after the trial ended (18 month follow up period) | | Intervention facilities: APR 84% (1,171 out of 1,400) at baseline, 37% (515 out of 1,380) at 6 months, and 54% (2,748 out of 5,084) at 18 months  Control facilities: it was 76% (1,063 out of 1,400) at baseline, 77% (1,084 out of 1,400) at 6 months, and 75% (2,772 out of 3,685) at 18 months  Adjusted: 18-month intervention-arm reduction in the APR of −36 pp (95% CI −55 to −17; P < 0.0001) | | Sustained reduction 18m after AMS bundle implemented |
| Wei X, Zhang Z, 201721 | 1. APR – cluster level proportion of antibiotic prescription for URTI in final 3 months of 6-month intervention period  Secondary:  A) more than one antibiotic B) any broad-spectrum antibiotic(s), and C) any intravenously administered antibiotic(s).  D) the full prescription cost (including the total of any consultation costs) | | APR individual level: intervention 🡪 82% to 40%; control 75% 🡪 70%  Intervention effect (ARR in antibiotic prescribing) after adjustment for: baseline APR, stratum (county), and potentially confounding patient and prescribing covariates = - 29% (95% CI -42 to -16; p=0.002)  No effect on multiple antibiotic prescribing rate, broad spectrum antibiotic prescribing rate or IV APR  No difference in crude antibiotic cost (p= 0.0004) | | Pragmatic AMS targeting providers and caregivers substantially reduced APR for childhood URTI |
| Zhang Z, 201825  (*Cost-effectiveness of study 21)* | | Incremental cost-effectiveness ratios (dividing the mean difference in cost of the two trial arms by the mean difference in APR) | | incremental cost of $0.03 per percentage point reduction in antibiotic prescribing. In addition to this incremental cost, the cost of implementing the intervention, including training and materials delivered by township hospitals, was $390.65 (SD $145.68) per healthcare facility. | Apart from upfront cost of $390USD, AMS bundle cost was “close to cost-neutral” | |
| Zhang, Chen, Chen, 201826 | 1. consumption of antibiotics  2. defined daily dose (DDD)  3. isolation of multidrug-resistant organisms (MDRO) and resistance rate of antibiotics | | All p<0.001  DDDs: 56,725 in 2011 to 31,380 in 2014  antibiotic use density (AUD) reduced from 93.8 to 43.5  antibiotic costs per patient (per quarter) decreased from 637 (± 29) RMB to 462 (± 49) RMB  Multidrug-resistant organisms isolation reduced from 463 (20.0) to 216 (6.9%)  Reduced resistance rate of general spectrum antibiotics for E. Coli, Kleb pneumo, Strep pneumo  DDD of carbapenem halved, with a significant reduction in infection or colonization with carbapenem resistant Acinetobacter baumanii r = 0.926, P < 0.001 | | implementation of ASP led to reduced medical expense, and decrease of improper use of antibiotics, and reduced antibiotics resistance rate and MDRO isolation |
| Zou, 201527 | 1. Antibiotic use, 2. Antibiotic indication; prophylaxis vs. treatment   Antibiotic type | | 67 (99%) vs. 30 (18%); P<0.001  Prophylaxis: 56 (84%) vs. 4 (13%) ; P<0.001  Treatment: 11 (16%) vs. 26 (87%)  Aztreonam: 45 (63%) vs. 4 (12%) | | AMS bundle resulted in reduction in number of children prescribed prophylactic antibiotics after successful air enema reduction |
| Ruvinsky, 201430 | Adequate antibiotic Rx according to hospital guidelines | | Adequate 21.57% vs. 35.6% (OR: 0.50 [0.35-0.70], p < 0.01) | | intervention based on an educational program reduced the proportion of inadequate antibiotic use from 35.6% to 21.6% |
| Chowdhury, 201931 | 1. Change in antibiotic use for complicated / uncomplicated ARI. 2. Consistency of advice given by pharmacists for antibiotic administration.   Reported reasons for not following guideline. | | 1. Decrease in prescribing antibiotics for uncomplicated ARI in children; Before 60/200 (30%) v 39/188 (21%) p<0.04. 2. No change in use of antibiotics for complicated ARI in children. Before 15/100 (15%) versus 16/100 16%, p=0.6   The intervention led to a decrease in the number of drug sellers recommending taking antibiotics in line with physician’s advice 11% v 0% (p<0.001) and advise to take antibiotics if not improved 39% v 7% (p<0.001) | | Very high risk of contamination.  Overall profit and patient request for antibiotics led to inappropriate prescribing and advice despite intervention highlighting issue with unregulated prescribing. |
| Sultana, 201732 | 1. Proportion of admitted patients on antimicrobials 2. Overall use of Cefixime, Ceftriaxone, Cefuroxime, Co-amoxiclav and Metronidazole in (DDD/100 bed days) 3. Use of individual anti-microbials as DDD/admitted patient who received an antimicrobial 4. Coverage of guideline   Adherence to guideline | | Results from Pediatric Department only.   1. Decrease in overall number of antimicrobial prescriptions in Department of Pediatrics. Before (30/60) 50% v After (30/75) 40% p<0.01 2. Ceftriaxone: Before 26.7 v After 10.7 DDD/100bed days, p<0.01   Cefuroxime: Before 5.0 v After 4.0  Ciprofloxacin: Before 18.3 v After 12.0  Flucloxacillin: Before 15.0 v After 1.3, p<0.001   1. Ceftriaxone: Before 4.6+/-6.5 v After 6.0+/-5.1 DDD consumed per patient   Cefuroxime: Before 14.1+/-5.4 v After 16.8+/-17.5  Ciprofloxacin: Before 2.4+/-0.8 v After 2.3+/-0.8  Flucloxacillin: Before 2.7+/-2.0 v After 3.0+/-0.0,   1. 22/30 (73.3%)   19/22 (86.3%) | | There was a high risk of contamination and the intervention time was short (15 days) with an undefined period for data collection before or after. |
| Calil 200137 | occurrence of nosocomial infections caused by multi-resistant bacteria | | Pre-intervention: 9/31 (29%) colonization with MDR E. Cloacae  Post-intervention: 37/342 (10.8%) colonization with MDR E. Cloacae  In the third phase, for 6 months, only 2 patients were colonized by multi-resistant E cloacae. In the fourth phase, the analysis of bacterial resistance profile indicated a reduction of nosocomial infections due to multi-resistant bacteria from 18 cases in 1995 to ‘average’ 2 cases per year until 1999 (range not given) p-values not given. | | Infection control education, antibiotic restriction was effective at reducing MDR E. cloacae colonization rate and MDRO infection rate |
| Gonzalez Ochoa E, 199638 | Number of antibiotic (over) prescriptions for mild ARI episodes | | Overprescription % by quarter:  Area A: 26.6% 🡪 31.1% 🡪 14.3% 🡪 7.8%; RR of 0.38 (95% CI = 0.21-0.66),  Area B: 20.6% 🡪 10.5% 🡪 13.3% 🡪 11.7%  Area C: 11.4% 🡪 12.2% 🡪 11.3% 🡪 12.3%  Area D: 19.6% 🡪 10.6% 🡪 23.6% 🡪 20.3% | | Resource intensive intervention  High risk of bias as data was collected from parental survey  Small numbers  Training and parental education reduced prescriptions for mild ARI, more than parental education alone |
| Murni I, 201539 | 1. proportion of patients with an HAI.  Secondary:  A) proportion patients exposed to inappropriate antibiotic use  B) HCW hand-hygiene compliance  C) mortality rate | | HAI risk pre vs. post: 22.6% (95% CI 20.3%- 24.9%) vs. 8.6% (CI 7.3% to 10.2%): RR 0.38 (95% CI 0.31 to 0.46)(p<0.01)  APR: no change, 63.6% vs. 62.2% (p=0.43)  Inappropriate prescription: 43% vs. 20.6% RR 0.46 (95% CI 0.40 to 0.55)  Hand hygiene compliance: 18.9% vs. 62.9 p<0.001  Mortality: 10.4% (95% CI 8.8 to 12.3%) vs. 8% (95% CI 6.7 to 9.6%)(p<0.05) | | Multi-faceted intervention successful at reducing HAI, appropriate antibiotic prescription and hand hygiene compliance, and mortality. |
| Opondo, 201141 | No. of patients receiving  antibiotics for inappropriate  indication | | 313/594 intervention group; 437/566 in control group  ARR for receiving antibiotic for inappropriate indication (95% CI) 0.41 (−0.06 to 0.88) p=0.08 | | Training health workers on the use of evidence-based guidelines for acute non-bloody diarrhea, audit and feedback to prescribers was effective in reducing number of inappropriate prescriptions |
| Haque, 201744 | | Days of therapy  Mortality  Antibiotic utilization  Appropriate use of antibiotics for culture negative like symptoms.  Cost of antibiotics | | DOT/1000patient days was 3447 and 1323 in the pre-ASP vs ASP periods (P<0.0001). 64% reduction in antibiotics utilization in ASP period. Mortality was 16.2% and 15.7% during the pre-ASP and ASP period, respectively (no p value)  The appropriate use of empirical antibiotic therapy for culture-negative infection-like symptoms (duration ≤2 days) increased from 6% (8/135) to 45% (57/127) (P<0.0001).  The DOT of colistin remained same during both the periods (DOT=115 vs 100, P=0.70).  COT decreased from US$22 125 in the pre-ASP period to US$9296 in the ASP period (P<0.0001) with cost reduction of 58%. | Positive impact of pharmacist-led daily audit and feedback ASP in reducing APR and cost. Short follow up period only (3 months). | |
| Kalaba M, 201846 | | 1. Combined antimicrobial utilization data with cumulative resistance in 2010 versus 2014  2. Cost per DDD | | MRSA: ‘general downward trend’ from 13.3% in 2010 to 3.8% in 2011, 0% in 2012, 6.7% in 2013 and 0.5% in 2014; no p value. The rate of ESBL-producing E. coli did not appreciably change during the study period, no p value.  49.4 and 27.8 DDDs/100 bed days in 2010 versus 2014 and associated reduction total costs per DDD for every antibiotic (p value not provided)  Significant missing data for resistance rates Cost per DDD ‘typically’ decreased, p values not provided | Reduction in drug utilization, reduction in MRSA, no change in ESBL E. Coli, no p values so unable to draw conclusions. | |
| **Guideline or policy implementation** | | | | | | |
| Liang, 201416 | | 1. % reduction/month in proportion of patients receiving injectable antibiotics, 2 or more antibiotics,  2. change in type of antibiotics prescribed  3. reduction in cost  (12 m f/up) | | No effect in 0-1 yr old age group  Intervention vs. control CHC monthly proportion of patients receiving an antibiotic injection and proportion receiving two or more antibiotics conditional on receiving an antibiotic decreased 9.17% and 7.34%, respectively (P < 0.01 or P < 0.05), however baseline APR markedly different between intervention and control CHC which is not accounted for.  Overall antibiotic prescribing not different before or after intervention.  There was a 10% reduction in average cost of antibiotics prescribed per patient (p=0.028) | Reduction in antibiotic use with government reform between intervention and control hospitals however baseline prescribing rate markedly different so impact of policy introduction uncertain. | |
| Zhang, Shen, Wang 200824 | | Defined Daily Doses and Drug Utilization 90%  Antibiotic consumption and resistant rate in one of the hospitals | | Overall antibiotic use in hospital A decreased by 42.7% during the intervention period (p=0.012). Decreasing trends also found in hospital B (11.1%, p=0.07) and hospital C (15.2%, p=0.068).  1st generation cephalosporin use decreased by 34.1% (p=0.031), 3rd generation cephalosporin use increased year by year | Significant reduction in antibiotic consumption in one hospital, with decreasing trends in other hospitals  Decrease use of narrow spectrum antibiotics and increase in broad spectrum antibiotics | |
| Zhan, Chen, Chen 200826 | | Defined Daily Doses (DDD)/100 bed days  Type of antibiotics used | | Defined Daily Doses (DDD)/100 bed days: 68.2 in 2002, 65.6 in 2005, 49.9 in 2006; by 2006 antibiotic use had decreased by 22.6% ( p = 0.042).  Antibiotic use density differed between hospitals located in the northern region and southwestern and southern regions.  The reduction in overall antibiotic consumption mainly resulted from reduction in penicillin (by 23.3%). | Policy change occurring in Oct 2004 eventually resulted in overall reduction in antibiotic use in 2005 however there was a wide variation in APR between different hospitals, therefore the impact of policy introduction is uncertain. | |
| Jinka D, 201733 | | 1. Antibiotic consumption DDD/100 patient-days one year after intervention   Secondary:  A) proportion of admitted newborns on any antibiotics B) choice of antibiotic C) overall mortality D) sepsis-related mortality | | 12.47 (pre) vs. 11.47 (post) DDD/100 patient days; p = 0.57  A) 58% (pre) vs. 46% (post); p<0.001  B) Ampicillin and gentamicin 66% (pre) vs. 84% (post) p <0.001  Third generation cephalosporin 1.45 (pre) vs. 0.45 (post) DDD/100 patient-days; p=0.002 Proportion babies on colistin and ciprofloxacin increased significantly (based on susceptibility results)  C) mortality 4% (pre) vs. 3% (post); p=0.1  D) sepsis related mortality 3% (pre) vs. 2% (post); p=0.28 | 1o No change in overall antibiotic consumption.  2o Reduced proportion newborns on any antibiotics on admission, and decreased consumption of third generation cephalosporins without reduction in mortality | |
| Murki, 200934 | | 1. Rates pf any antibiotics and individual rates of cephalosporin, aminoglycosides, ampicillin, ciprofloxacin, pip-taz and meropenem.  2. Rates of ESBL and proportion of gram negative bacteria resistant to individual antibiotics. | | 1. All antibiotics 324(31%) v 376(35%), p=0.05   Any cephalosporin 165(15.8%) v 32(3%) p<0.001  Amikacin/gentamicin 228(21.8%) v 296(27.6%) p=0.002  Ampicillin 133(12.8%) v 296 (25.7%), p=0.002  Ciprofloxacin 36(3.4%) v 79 (7.3%) <0.001  Pip-Taz 42(4%) v 51 (4.8%), p=0.4  Meropenem 26(2.5%) v 32(3%), p=0.48   1. ESBLs 15(47%) v 14(25%), p0.035   Amikacin 10 (31%) v 11 (20%) , p=0.21  Cefotaxime 26 (81%) v 29 (51%), p=0.006  Ciprofloxacin 18 (56%) v 16(29%), p=0.01  Pip Taz 11 (34%) v 10 (18%), p=0.08 | High risk of contamination between examination phases. Good description of baseline characteristics illustrates significant increase in CPAP and Central line use in the post-intervention phase.  No description of how ESBL status or resistance was defined in the laboratory setting.  1. reduction in cephalosporin use.  2. increase in amikacin and ciprofloxacin use.  3. decrease in incidence of ESBL producing bacteria despite increase in incidence of GNB sepsis. | |
| Lee 200742 | | 1. reduce extended spectrum cephalosporin use  2. prevalence of ESBL *K. pneumoniae* and *E coli* from sterile sites  3. change in the clinical outcome of invasive diseases caused by *E. coli or K. pneumoniae* | | - piperacillin/tazobactam use increased from 2.2 to 108.0 days on antibiotics/1000 patient admission days/year (AD) (P for trend < 0.001)  - extended-spectrum cephalosporin use decreased from 175.0 to 96.9 AD (P for trend < 0.001).  - ESBL prevalence decreased; 39.8% (41/103) during pre-intervention, 35.7% (25/70) during transitional period and 22.8% (18/79) after intervention.  -decreasing trend of ESBL production was more evident for *K. pneumoniae* (64.1% to 25.6%; P for trend < 0.001) than *E. coli* (25.0% to 19.4%; P for trend = 0.514).  - *A. baumannii, Enterobacter spp. and P. aeruginosa*, 107 strains available for analysis during entire study period with no increase in tazobactam resistance post intervention  - The mortality rates of invasive disease caused by *E. coli or K. pneumoniae* remained unchanged. | The substitution of piperacillin/tazobactam for extended-spectrum cephalosporins decreased the prevalence of ESBL production of K. pneumoniae more than E. coli. Mortality rates of invasive disease from these organisms remained unchanged. | |
| Berild, 200845 | | 1. APR   Secondary:  A) mortality  B) duration of fever  C) duration of hospital stay  D) cost | | A) Gastrointestinal infection (GII) intervention group % received antibiotics: 94% in 2002, 41% in 2003, 73% in 2004.  Respiratory tract infection: 90% in 2002, 53% in 2003, 83% in 2004.  Proportions of patients who received antibiotics in 2004 lower than in 2002: risk difference GII RD = 0.217 (P ≤ 0.001), RTI RD = 0.073 (P = 0.013) Secondary  A, B, C) There was no difference in mortality, duration of fever or duration of hospital stay between the intervention and control wards (descriptive results only).  D) 16% reduction in average cost per patient on GII ward, 38% increase on resp ward, no p values provided | Unsustained reduction in antibiotic prescribing 1 year after intervention.  High risk of contamination so unable to interpret intervention vs. control group APR. | |
| **Clinical decision tool** | | | | | | |
| Wu, 201722 | | reduction of the duration of antibiotic treatment  2. A/E from abx  3. Length of hospital stay | | Prescription rates and antibiotic exposure in the PCT group were decreased compared to standard group: from 83.91 to 54.64% (p>0.05) and 6.66 ± 5.59 to 3.98 ± 2.17 days (p values not provided), respectively  Clinical outcomes (2 and 3) no difference between groups: The length of hospital stay was not significantly different between the PCT (9.96 ± 5.81 days) and standard groups (10.58 ± 4.24 days) (difference: –0.62%; 95% CI: –1.68 to 0.43), no p values  Antibiotic adverse events 22.9% PCT group vs 29.1% standard group OR 0.72 (0.45, 1.16), no p values | Procalcitonin guided treatment of LRTI reduced antibiotic prescription and duration of antibiotics *(not statistically significant)* | |
| Torres, 201429 | | 1. Proportion of patients receiving abx initially  Secondary  2. clinical outcome to day 10 | | 28/60 bacterial pneumonia score group vs 52/60 standard care group received abx p<0.001  Clinical outcome unfavorable 5/60 vs 5/60 (> 48hr fever, 2 in each group hospitalization, nil ICU or death). | Application of a bacterial pneumonia score reduced antibiotic prescribing without changing overall clinical outcome | |
| Keitel, 201735 | | 1. Clinical outcome by day 7 f/up  Secondary  A) Proportion of antibiotic prescription on day 0 and between day 1 and day 6,  B) primary referrals  C) severe adverse events by day 30 (secondary hospitalizations and deaths) | | 2.3% (37/1,586) of patients experienced clinical failure by day 7 in the e-POCT arm versus 4.1% (65/1,583) of patients in the ALMANACH arm (RD −1.7, 95% CI −3.0, −0.5; RR 0.57, 95% CI 0.38, 0.85) There was a 49% lower relative risk of clinical failure in the e-POCT arm compared to routine care (RR 0.51, 95% CI 0.31, 0.84; RD −2.3, 95% CI −4.2, −0.4))  Antibiotic prescription lower in ePOCT (11.5%) vs. ALMANACH (29.7%) (RR 0.39, 95% CI 0.33, 0.45, p < 0.001).  In the e-POCT arm, 11.5% (182/1,586) were prescribed an antibiotic at day 0, versus 29.7% (470/1,583) in the ALMANACH control arm (RR 0.39, 95% CI 0.33, 0.45; p<0.001) | point-of-care tests: oximetry, hemoglobin, C-reactive protein, and procalcitonin reduced antibiotic prescribing compared to traditional reference algorithm (ALMANACH); and improved clinical outcome | |
| Shao, 201536 | | 1. proportion of children cured at day 7 and who received antibiotics on day 0 | | Cure on D7 815/838 (97.3%) vs. 573/623 (92%); P<0.001  Antibiotics prescribed D0 130/842 (15.4%) vs. 525/623 (84.3%); P<0.001  Cumulative proportion of children prescribed antibiotics over the whole 7 day follow-up period was 19.0% in the intervention versus 87.5% in the control arm (p<0.001) | When strictly applied intervention resulted in better clinical outcome than standard practice, and in 70% reduction of antibiotics prescribed to children with acute illness | |
| Bucher, 201243 | | RR of receiving antibiotics | | 29/100 in fecal leukocyte + rotavirus rapid test group; 50/101 in fecal leukocyte test only group (RR: 0.59; 95% CI: 0.41 to 0.84 p=0.03) | rapid test for rotavirus was associated with fewer patients receiving antibiotics for acute diarrhea | |
| Ozkaya, 200947 | | RR of receiving antibiotics | | 34/50 in influenza rapid diagnostic test group vs. 47/47 in routine care group  RR= 0.68 (0.56 to 0.82) p=0.01 | Antibiotic prescription was prevented in just 32% of patients with a positive rapid influenza test | |
| Do NT, 201648 | | 1. Number of patients receiving any antibiotic within 14 days  Secondary:  abx activity in urine (D3, 4, 5), immediate abx prescription, subsequent abx use, prescription on second visit, source of abx not prescribed at enrolment, frequency of reconsultation, hospital admission or death, time to resolution of symptoms | | Abx prescription within 14 days:  295/448 (65.8%) vs. 374/487 (76.8%) OR (95% CI) 0·55 (0.41–0.75) p< 0·0001  Immediate abx prescription:  227/510 (44·5%) vs. 333/518 (64·3%) OR (95% CI) 0·39 (0·30–0·52), p<0.0001  Subsequent abx use similar:  68/221 (30·8%) vs. 41/154 (26·6%) OR (95% CI) 1·22 (0·78–1·94) p = 0.38  No significant differences in other secondary outcomes | Overall POC CRP testing reduced antibiotic prescribing rate for acute non-severe respiratory tract infection, however there was significant heterogeneity among the primary health care centers | |
| **Antibiotic restriction and financial disincentive** | | | | | | |
| Gong, 201615 | | 1. Monthly average use of abx  2. Expenditure on abx relative to all other medications | | Outpatients: reduction = 59.4%; β = −1.235, P < 0.001, monthly trend +0.043; immediate reduction in expenditure by 46.7% (p<0.01)  Inpatients prescribed antibiotics: 40% in the pre-intervention group, to 34% after the implementation of prior authorization alone, and to 23% after adding financially punished audit and feedback (χ2 = 3.0 × 103, P < 0.001); immediate reduction in expenditure by 16.3% (p<0.01)  Effect not sustained - +3.4% per month trend in prescribing during 2nd intervention period (NS) | Prescribing restrictions in addition to audit and feedback with financial disincentive resulted in reduction in APR which was sustained for carbapenems but not clearly for other antibiotic classes in inpatients. | |
| Xu, 201923 | | 1. Antibiotic usage  2. MDR-GNB detection rate (colonization vs infection not stated) | | All p<0.01  pre-intervention 2010  outpatient: 57.8%  ED: 77%  inpatient: 76.9%  AUD inpatient: 38.89  AUD 3GC: 14.96  AUD carbapenem: 1.77  Detection rate ESBL E. coli: 74.2%  Detection rate ESBL KP: 78.7%  Detection rate CRAcB: 14.9%  Detection rate CRPsA: 12.3%  2011-2014  outpatient: 53%, 44.5%, 31.7% per year  ED: 74.4%, 69.1%, 53.8% per year  inpatient: 74.5%, 51.9%, 55.2% per year  AUD inpatient: 38.3, 32,82, 30.96 per year  AUD 3GC: 12.73, 10.63, 11.74 per year  AUD carbapenem: 2.11, 1.81, 1.73 per year  Detection rate ESBL E. coli: 76.5%, 70.8%, 62.7%  Detection rate ESBL KP: 78.7%, 68.3%, 66.8%  Detection rate CRAcB: 35.8%, 29.5%, 23.8% per year  Detection rate CRPsA: 10.2%, 15.9%, 21.9%  2014-2017  outpatient: 29%, 24.7%, 23.5% and 22.8% per year  ED: 47.3%, 39.7%, 36.7%, 33.6% per year  Inpatient: 49.4%, 50.5%, 49.6%, 51.2%  AUD inpatient: 25.88, 17.29, 19.14, 19.66 per year  AUD 3GC: 6.68, 5.83, 6.83, 6.85 per year  AUD carbapenem: 1.95, 1.80, 2.07, 1.80 per year  Detection rate ESBL E. coli: 62.4%, 52.3%, 47%, 46.5%  Detection rate ESBL KP: 53.8%, 43.8%, 31.8%, 33.1%  Detection rate CRAcB: 30.8%, 19.4%, 12.9%, 10.9%  Detection rate CRPsA: 11.9%, 15.3%, 8.5%, 5.4% | Sustained decrease in antibiotic usage year on year after introduction of antibiotic policy including financial disincentive  Reduction in MDR-GNB rate achieved | |
| **Audit and feedback on restricted antibiotics** | | | | | | |
| Rahbarimanesh, 201940 | | 1. Appropriate use of vancomycin and meropenem  2. mortality rate  3. antibiotic prescription  4. antibiotic dose  5. antibiotic duration  6. length of hospital stay  7. positive blood cultures | | % prescriptions pre vs. post: MPM 10.44% vs. 1.47% and VMN 35.52 vs. 4.41% (p <0.05)  mortality rate: 28.4% vs. 5.9% (p=0.001)  Reduction in positive BC: 23.88% vs. 4.41% (p=0.01) mortality rate was significantly reduced from 28.4% in 2014–2015 to 5.9% in 2015–2016 (p=0.001).  Length of stay: 22.7 ± 1.9 to 15.6 ± 2.8 p=0.015 Antibiotic dose: 23.36 ± 3.8 to 10.90 ± 3.6 p=0.043   1. Antibiotic duration: 11.9 ± 9.5 to 7.4 ± 4.6 p=0.01 | Reduction in vancomycin and meropenem use post ASP and reduction in mortality however this was in conjunction with marked reduction in rate of positive BC in this hospital | |