



Policy Research Paper №62

Reasons of increased incidence of acute enteric infections of unknown etiology

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Abbreviations

DSES	Department of Sanitary and Epidemiological Surveillance under MoH KR
RCSSES	Rayon Center of State Sanitary and Epidemiological Surveillance
MoH KR	Ministry of Health of the Kyrgyz Republic
ND	Normative documents
PP	Pharmaceutical products
CG/CP	Clinical guidelines/clinical protocols
AEI	Acute Enteric Infections
TH	Territorial Hospital
FMC	Family Medicine Center
FAP	Feldsher-midwife station

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1. Introduction

In the structure of infectious diseases of Kyrgyzstan for 2008 Acute Enteric Infections (AEI) made up 34,6% and its specific gravity held the first place among all infectious diseases. Multiyear analysis of incidence rate showed that over the last 10 years there were registered from 12 thousands up to 45 thousands of cases of intestinal infections throughout the Republic and more than 80% of them fell at children under 14 years. AEI incidence rate till recently had a tendency for decrease from 369,2 (an indicator per 100.000 population) in 1995 till 249,7¹ in 2003. Mortality rate among children under 14 also have been decreasing from 340 in 2004 till 151 children in 2008.

In spite of relatively favorable situation in regards to mortality rate from AEI, AEI incidence rate has increased over the last 5 years. At that the increase of AEI of unknown etiology has increased by 2,2 times from 152,2 in 2004 up to 347,1² in 2008. The main structure of intestinal infections composes of enteritis of undefined etiology, which make up 64,7%, the defined etiology makes up 25% and dysentery makes up 13,3%.

Annually about 100 children under 14 die from AEI of undefined etiology (109 children in 2003, 128 children in 2008). Incidence and mortality rates of AEI of unknown etiology may have consequences both for the health of population and health economics. For example, health care organizations of the Republic do not have efficient diagnostic tools and specific therapy to diagnose and treat AEI of viral etiology. Under conditions of restricted stay at hospital, the growth of this group of infections can negatively affect outcome of AEI cases of undefined etiology and efficiency of prevention of AEI of viral etiology.

Access to pure potable water, elibiotics and delivery of medical care are the most frequently mentioned factors that lead to AEI incidence and mortality. As to the last group of factors, it should be noted that after reorganization process started changes have taken place in the Kyrgyz health care system, which were designed to improve the situation with AEI. At all health care organizations of the primary level there were opened stations for rehydron intake of and clinical protocols for AEI were developed and mechanisms were established to remunerate medical workers and medical institutions for management of AEI cases and other. Undertaken measures and other processes can have consequences for distribution of roles among medical institutions in relation to management of AEI cases and lead to onset of new motives of behavior on part of medical workers and to changes in terms of opportunities to register AEI cases. For example, for today only in-patient cases are registered. Quite often patients that take treatment at home are left with AEI of undefined etiology.

Having said this, it is necessary to study reasons of increasing incidence of acute enteric infections of undefined etiology and to which extent measures undertaken by health organizations are efficient in terms of decreasing incidence of AEI of undefined etiology.

¹ Indicator for 100,000 of population

² Indicator for 100,000 of population

2. The goal of the research

To study reasons for and consequences from incidence of acute enteric infections of undefined etiology.

3. Objectives of the research

1. To review tactics of management of AEI patients and of existing clinical protocols and regulating instructions;
2. To assess the completeness of the system for registration of AEI at health care organizations at all levels;
3. To assess equipment status and activities of laboratories, engaged into diagnostic testing on AEI of unknown etiology;
4. To study practices used to establish diagnosis of AEI cases;
5. To study interaction among medical institutions upon management of AEI patients (FGP, FAP, TH, CSSES, bacteriological and virologic laboratories);

4. Research materials and methods

The research was conducted with the use of cross-over design. The analysis was conducted with the use of both quantitative and qualitative data. For data collection interviews were taken and normative documents were reviewed.

Records on registration of AEI cases, normative documents and instructions were reviewed at health care organizations, as well as accounting data and monthly reporting forms, related to AEI were studied at institutions that conduct diagnostic testing.

Interviews were conducted with:

- health care workers (heads of institutions, physicians of FGPs/FAPs and territorial hospitals and laboratory specialists);
- family physicians at 4 FGPs;
- bacteriologists from 6 bacteriological laboratories and City Centers for SSES and territorial hospitals;
- infectiologists from 4 territorial hospitals.

Interviewing of family physicians and in-patient physicians was conducted with the use of semi-structured questionnaires and focus-groups. Questions of the questionnaire developed to survey physicians were designed to analyze drugs taken by patients before visiting primary health care organization, prescription of antibacterial therapy and diagnostics and outcome of the treatment.

Bishkek City and Osh oblast and Chui oblast were selected in order to conduct the research and to get an insight into reasons of high AEI incidence rate of undefined etiology. In these regions over the last years the highest indicators have been shown for mortality and prevalence rates of AEI of undefined etiology.

In each region there were investigated institutions of primary level and in-patient level (infectious hospitals or departments) that treat AEI patients, Centers for State Sanitary and Epidemiological Surveillance and laboratories that diagnose AEI of undefined etiology.

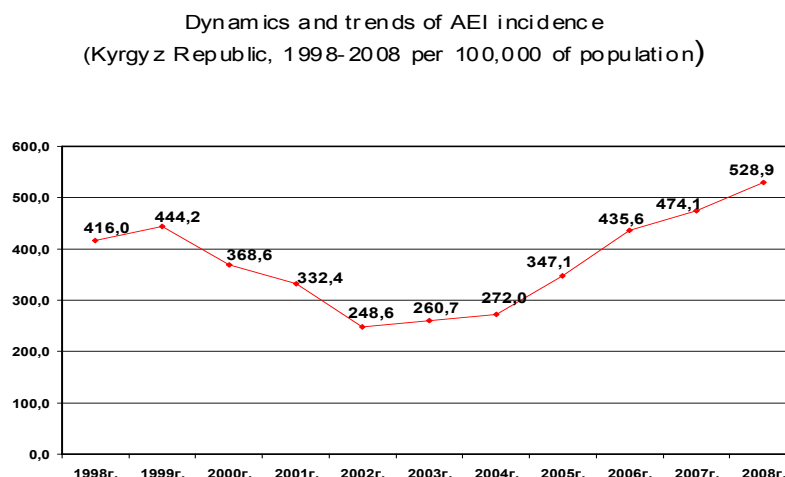
- Bishkek City (Republican Clinical Infectious Hospital, FMC №6, Bishkek Center for SSES)
- Osh oblast (Osh City, Uzgen rayon)
- Chui oblast (Issyk-Ata rayon)

In order to understand general factors related to incidence of the groups of enteric infections there were used multiyear data, entered into the State Statistical Form №1 «On infectious and parasitic diseases», approved by National Statistics Committee, as well as annual data on infectious and parasitic diseases collected at Central-Asian region and Russian Federation.

5. The review of the current situation with acute enteric diseases in the Kyrgyz Republic

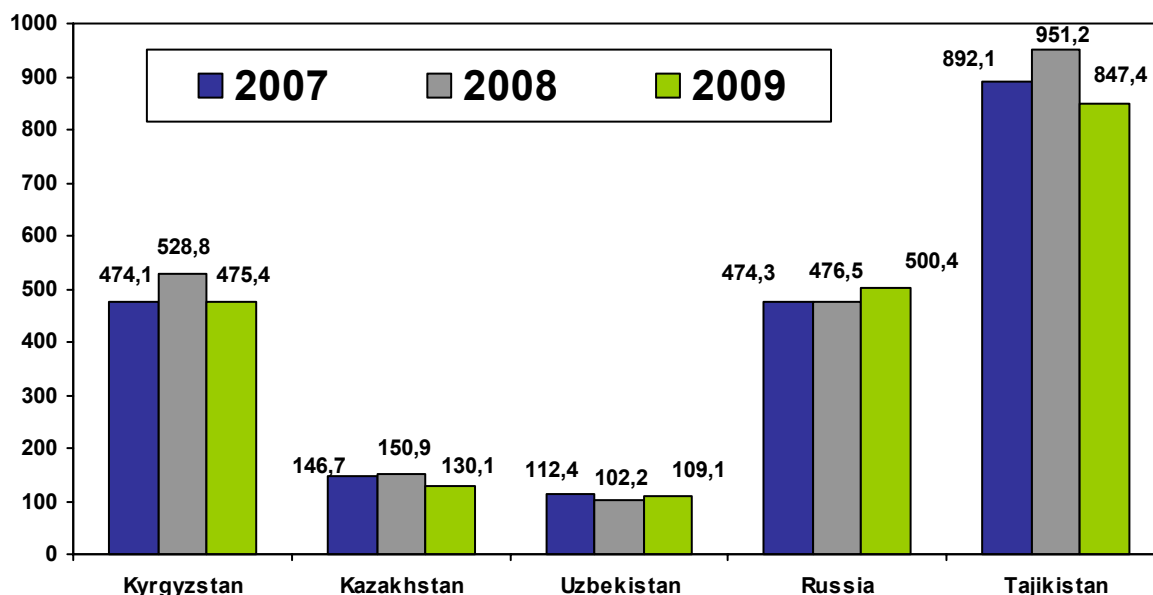
Analysis of AEI incidence data for the last 10 years from 1998 till 2008 shows that average country indicator for incidence of the group of enteric infections remains to be steadily high, in some years amounting up to the level of 260,7 (2003) and 528,9 (2008) per 100,000 of population (Figure 1).

Figure 1



Among countries of the Central Asia and Russian Federation, the Kyrgyz Republic holds leading position ceding only to Tajikistan (Figure 2). [Informational statistical data on infectious and parasitic diseases in Central-Asian region and RF, 2007-2008].

Incidence rate of the group of enteric infections in CIS countries for 2007-2008 (per 100,000 of population)



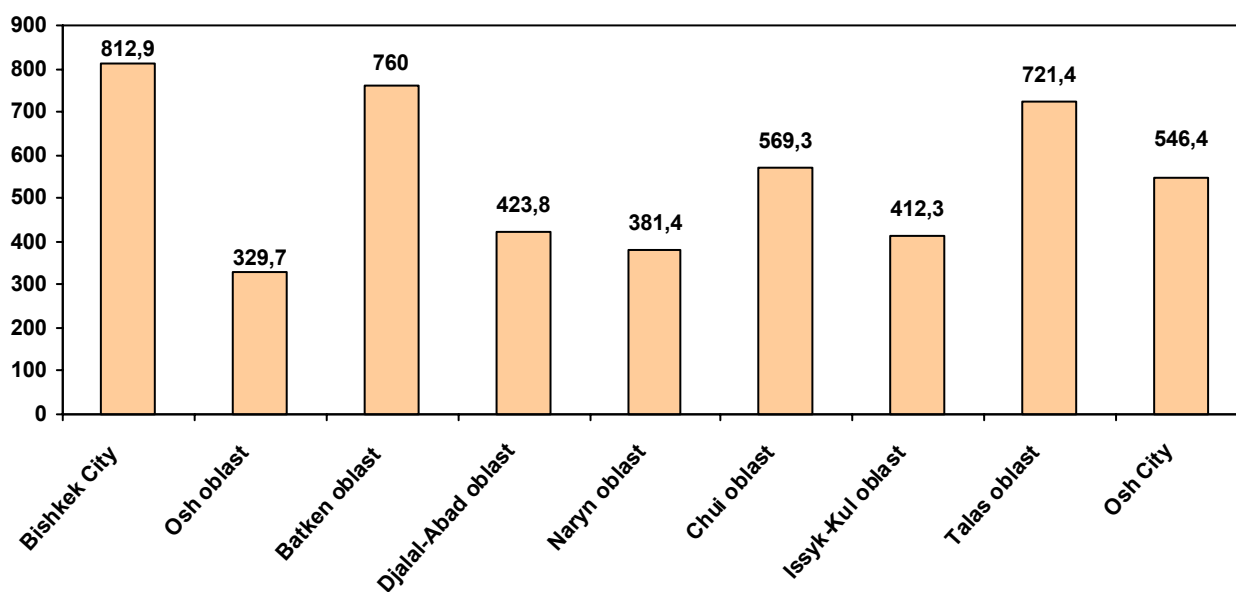
The analysis of multiyear dynamics of AEI incidence by regions of the Republic has shown territorial inequality in terms of the spread of these infections. The highest level of AEI incidence was noted in the southern region of the Republic (Osh oblast, Djalalabad oblast and Batken oblast), characterized by hot climate, high density of the population and high birth rate.

There was noted the considerable decrease of epidemic process of AEI in Naryn oblast: the average level of incidence rate in 2008 decreased by 1,5 times in comparison with the period of 1992-1993 and it was minimal.

The analysis of data on AEI incidence for 2008 has shown that AEI incidence was unequal in some northern oblasts of the Republic as well. Morbidity rate prevailed in Talas oblast and Bishkek City, where indicators made up 721,4 and 812,9 per 100,000 of population correspondingly (Figure 3). Epidemic security of mentioned natural and economic zone was determined by natural and climatic conditions, remoteness of settlements and lower influence of transmission through water and food than at other area of the Republic. Epidemiological forecasting in this area in terms of enteric infections assumed to be favorable: indicators per 100,000 of population are not of increasing nature and are lower than average republican incidence rate by 2,3 times.

Figure 3

**Incidence of AEI by regions of the Republic for 2008
(indicator for 100,000 of population)**

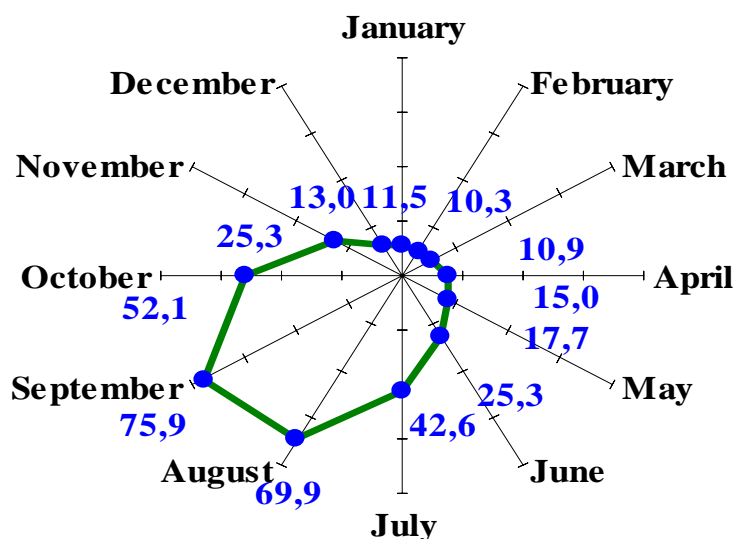


5.1. Seasonality of incidence of general enteric group

The analysis of general group of enteric infections showed that the lowest incidence indicators have been registered from December till April and then there was observed increased incidence from May till October. Maximal incidence rate fell at August-October, reaching its peak in September (Figure 4).

Figure 4

Seasonality of AEI incidence rate

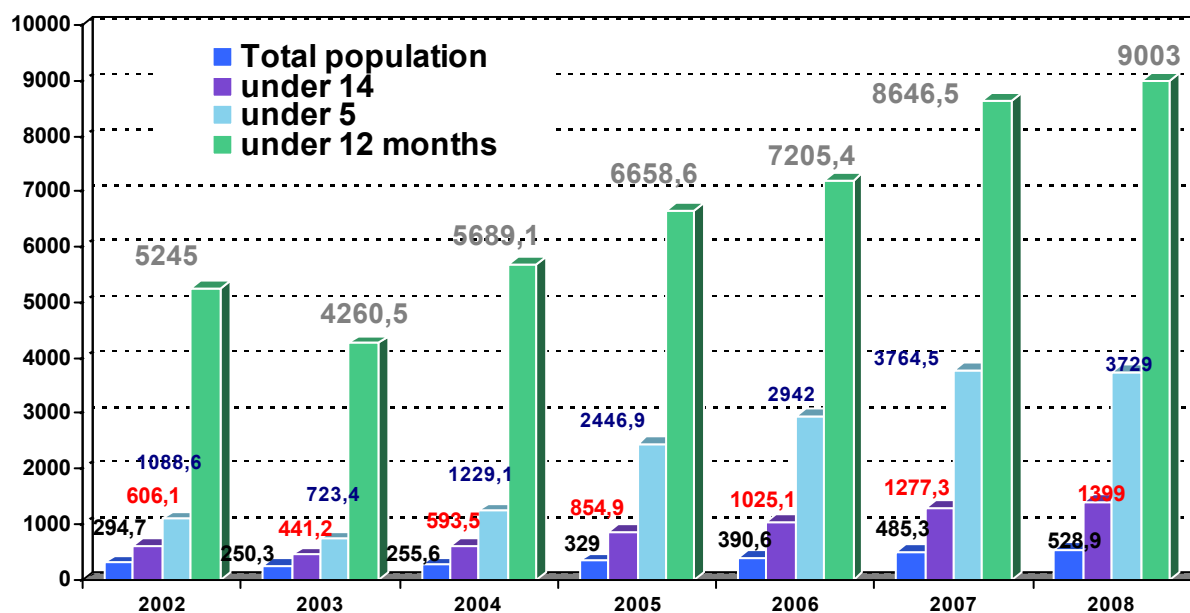


5.2 Analysis of age structure

Mainly children under 14 get sick with AEI. Main risk groups exposed to AEI of undefined etiology were children under 1: from 33,8% up to 45,4% from the number of registered cases fell at these age groups. Taking into account the fact that children of early age get predominantly afflicted with these diseases, it can be assumed that transmission ways of the infection go through contacts and food (Figure 5).

Figure 5

Multiyear AEI morbidity by age groups in the Kyrgyz Republic for 2002-2008 per 1000,000 of population



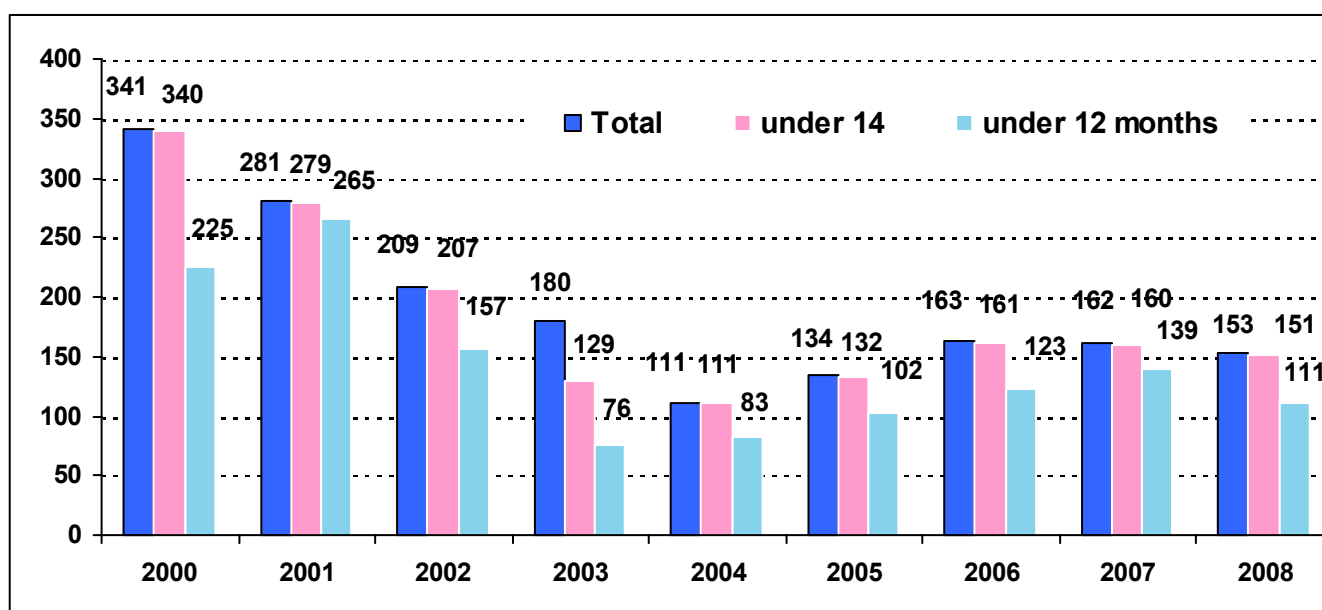
5.3 Mortality rate from AEI

At all age groups afflicted with AEI, the mortality rate from AEI of undefined etiology prevailed, which exceeded mortality rate from AEI of defined etiology in different years in the range from 1,47 times up to 4,85 times. The highest indicators of mortality were noted in the age group under 12 months. Thus, in 2008 the mortality rate from AEI of defined and undefined etiology among children under 12 months made up 0,19 and 0,78 accordingly throughout the Republic. While mortality rate among children in age groups of 1-6 years was considerably lower and made up 0,01 and 0,04 accordingly.

Mortality rate in southern oblasts of the Republic exceeded similar indicators in the northern regions of the country (Figure 6).

Figure 6

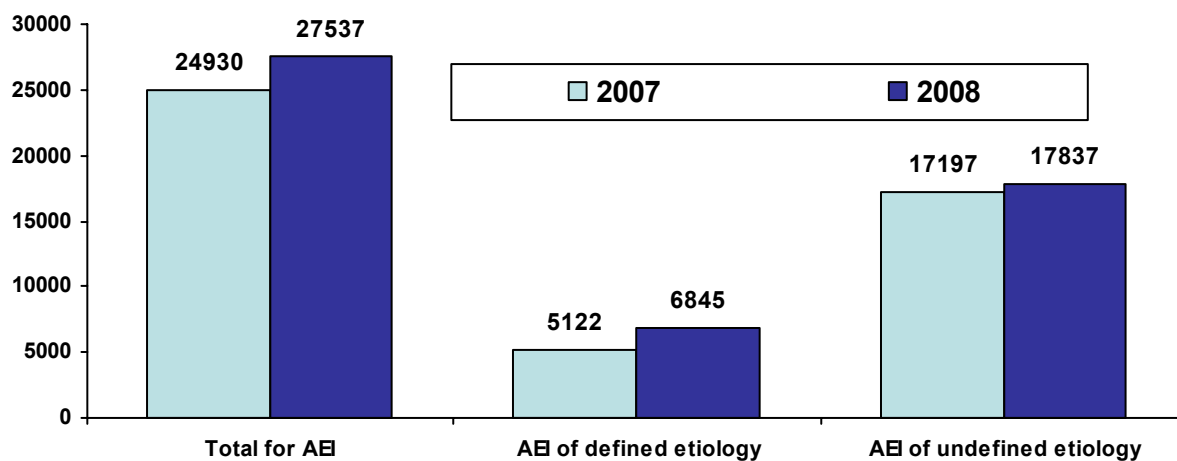
Mortality rate from AEI in the Kyrgyz Republic for 2000-2008



The structure of enteric infections for the greater part consists of enteritis of undefined etiology. In spite of insignificant improvement of etiologic decoding, morbidity rate of AEI of undefined etiology remains to be at high level. For the year 2008 the type of pathogenic activator was determined only in 24,8% of cases out of all AEI cases and in the rest of cases (64,7 %) the type of activator was not determined and accordingly it was diagnosed as AEI of undefined etiology (Figure 7).

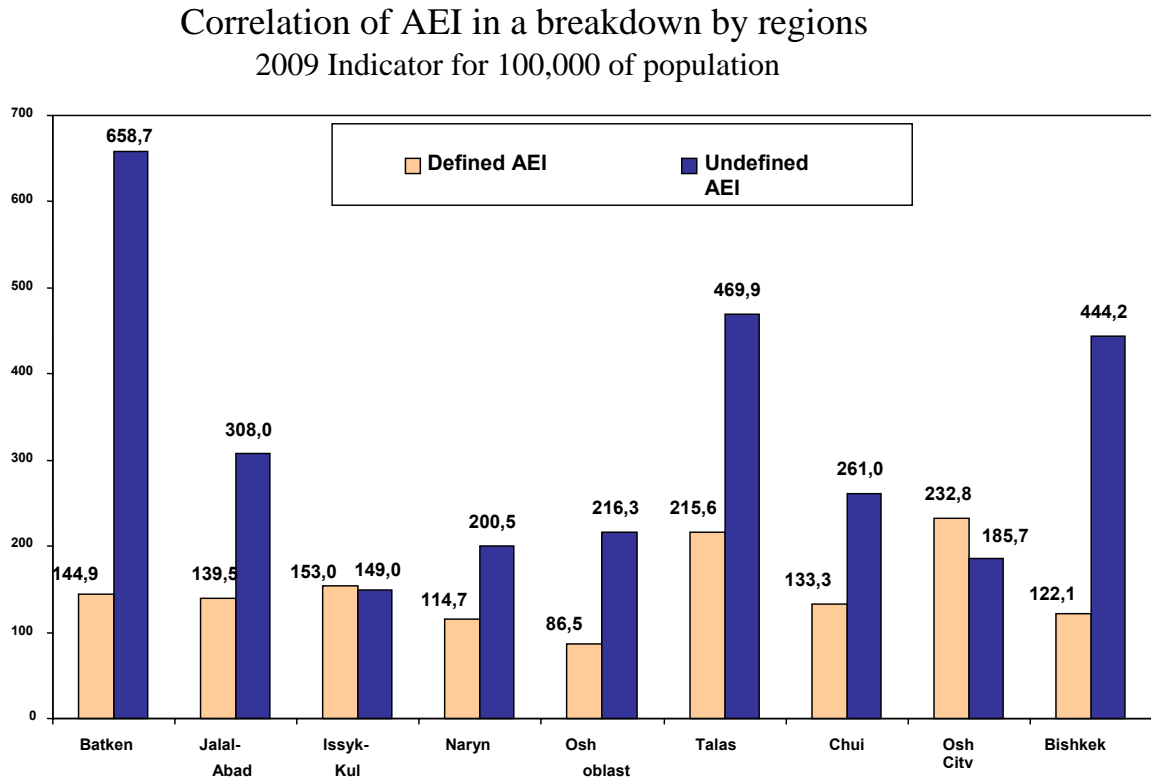
Figure 7

AEI correlation
The Kyrgyz Republic, 2007-2008



The analysis of correlation of AEI for 2009 in a breakdown by regions showed that the highest indicators of AEI of undefined etiology were reached in Batken oblast – 658, 7 (per 100,000 of population) and it has exceeded the indicator for AEI of defined etiology by 4,5 times. High indicators of correlation between AEI of defined and undefined etiology were also given in Bishkek City and difference made up 3,6 times. In Talas, Djalal-Abad and Osh oblasts correlation of AEI of defined and undefined etiology made up on average about 2,3 times.

Figure 8



6. Normative documents for registration and management of AEI patients

1. Registration of AEI cases is based on the following normative documents:

- The Law «On public health»
- The order of the Ministry of Health of the Kyrgyz Republic, № 610 from November 26, 2008 «In improvement of the system of sentinel surveillance over infectious diseases in the Kyrgyz Republic». This order regulates registration, reporting and submission of epidemiological data and registration of egested bacterios and so on.
- The order of the MoH of the KR, №307 from August 29, 2001 «On measures to control acute enteric infections in the Republic».

For registry and registration of AEI patients the statistical form №1 is maintained, which registers only those cases for which medical worker filed expedited report. Expedited report is submitted to territorial Center for SSES only for hospitalized patients with AEI and AEI patients treated at out-patient level are not reflected in statistics and are not taken into account.

2. Management of out-patients in regards to treatment and laboratory examination is conducted based on clinical protocol for the primary health care level titled as “Treatment of acute enteric infections” (Collection of clinical protocols №3, 2006).

3. Etiologic decoding of acute enteric infections is maintained by territorial bacteriological laboratories based on “Methodological instructions for microbiologic diagnostics of diseases, caused by enterobacterias”.

The analysis of existing treatment standards and normative documents on maintenance of epidemiological surveillance and AEI prevention showed that there were differences in approaches to diagnostics and treatment in normative documents that regulate management and treatment of AEI patients.

According to the order of the Ministry of Health of the Kyrgyz Republic from August 29, 2001, №307 «On measures to control acute enteric infections in the Republic» patients treated at home are not subject to bacteriological examination except of children visiting preschool institutions and persons involved into production and sale of food products. Medical workers of FGPs and FAPs select samples from mentioned patient population». Main points in the management of children with AEI (diarrhea) are rehydration therapy and nutrition...».

The clinical protocol specifies that «...bacteriological examination of feces is conducted among children from child welfare institutions of the closed-type or children visiting preschool institutions...». At the same time the section “Pharmaceutical Treatment” does not instruct to prescribe bacteriological examination for patients before prescribing antimicrobial agent.

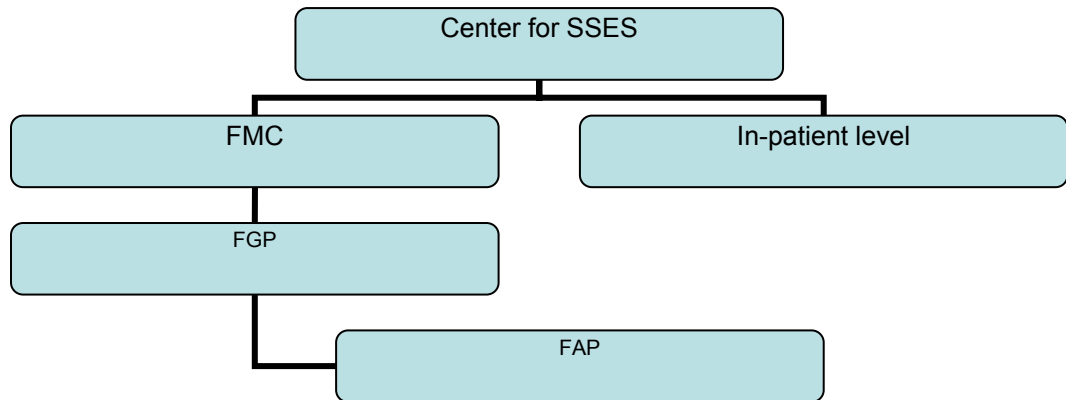
The clinical protocol specifies «...prescribe antimicrobial agent if feces contains mucus and/or blood. Antimicrobial agent of the first line is Ampicillin. Antimicrobial agent of the second line is nalidixic acid...». Moreover, primary health care organizations (FGPs, FAPs) do not have corresponding conditions to examine patients with diarrhea (test-tubes with transport media).

These facts indicate that it is necessary to review all normative documents that regulate treatment and management of AEI patients and to bring them into compliance.

7. Registration of AEI patients at the primary level

In case if the patient with AEI visits FAP the information about this case is submitted to FMC, where it gets aggregated and then transferred to the territorial Center for State Sanitary and Epidemiological Surveillance.

In case if the patient visits in-patient institution the information about his case is submitted as expedited report directly to the Center for SSES. In the rayon/city there may be few FMCs and in-patient institutions, which separately submit information to the Center for SSES, which is submitted further to the national level.



Based on their clinical conditions AEI patients are referred by FAPs to FGPs or in-patient institutions (for medical consultation or hospitalization) or stay at home. Statistical reporting is submitted by FAP feldsher to FMC at the end of each month.

At FMC level the data collected from all territorial FAPs gets aggregated and submitted further to the territorial CSSSES

The rayon data is submitted to territorial Center for SSES on monthly basis but these data is not included to the statistical reporting form.

In-patient data is also send as expedited report to the territorial CSSSES. Rayon or municipal sanitary services report to the republican level on monthly basis but only about those patients that were referred by expedited report. The registration scheme for AEI patients is given in the Attachment 1.

8. Opinion of physicians regarding delivered medical care to patients with enteric infections at out-patient level (focus-groups with physicians)

Interviews with family physicians from FMCs revealed that FMC doctors maintain AEI patients according to approved clinical protocol; however, antibacterial drugs are often prescribed without indications as physicians are not sure that patients or parents of sick children will strictly follow instructions (liquid intake, diet) and in order to avoid complications they prescribe antibacterial drugs right away. Upon detection of one of the indications for hospitalization the patient is urgently hospitalized to in-patient institution.

In those cases when parents if sick children refuse from hospitalization, the family physician sends expedited report to the territorial CSSSES and bacteriological laboratory examination is not prescribed to the patient and etiological structure is not decoded and the case is diagnosed as enteritis of undefined etiology.

Fragments from interviews with physicians:

«...when patients refer for medical aid I always prescribe antibiotics of cephalosporin range even if the child has mild disease and I do not indicate it in the medical card...»

(Osh City, FGP physician)

«If one child is prescribed to take ampicillin then in case of another child gets sick their mother will definitely give the same antibiotic and she will refer to a doctor only in case of aggravation»

(Uzgen rayon, FGP physician)

The focus-groups conducted with physicians showed that physicians preferred to prescribe antimicrobial drugs before bacteriological examinations are done, based on above-mentioned normative documents. Patients that were taking antimicrobial drugs independently without any improvement and who referred to physicians in aggravated state were hospitalized to in-patient care level. Henceforth, microbial agent is rarely plated from analyses of such patients.

Besides, in opinion of physicians when antimicrobial drugs of new generations are prescribed the recovery period of patients gets reduced, thus, decreasing the workload of medical workers (observation of contact people, patronage and so on).

Family physicians also noted that patients stay from 10 till 30 minutes at oral rehydration units (ORU) and not more than that. Liquid intake at ORU a formality and it is only about issue of rehydration powder. It should be noted that ORU were opened at all FMCs but did not work appropriately. Medical nurses of each FGP could easily issue powders and train mothers on how to prepare solutions.

9. Review results of out-patient medical cards and clinical records анализа

9.1. Review of out-patient medical cards with AEI diagnosis at primary level

Review of out-patient medical cards with AEI (forms U25 and 112) showed that

- quite often patients with diarrhea were taking antimicrobial drugs independently without prescriptions (20%),
- in more than a half of examined cases (52%) patients went to ORU (Oral Rehydration Unit)) where they have received recommendations on administration and preparation of rehydration powders;
- only in 5% of examined cases family physician prescribed bacteriological testing before prescribing antibiotics;
- in 43% of examined cases family physician prescribed to AEI patients to take antimicrobial drugs without preliminary laboratory testing;
- in 15% of examined cases patients that received out-patient treatment had aggravated state and complications and were referred to in-patient care. (Table 1).

Table 1.

Management of out-patients with AEI at the primary level

Regions	Independent treatment before visiting FGP	Liquid intake at ORU	Prescription of bacteriological examination	Additional prescription of antibiotics	Treatment outcome (referred to in-patient treatment)
Osh City	10% (n-10)	50% (n-10)	20% (n-10)	60% (n-10)	10% (n-10)
Uzgen rayon, Osh oblast	30% (n-10)	70% (n-10)	-	30% (n-10)	-
Bishkek City	-	40% (n-10)	-	40% (n-10)	30% (n-10)

Issyk-Ata rayon, oblast	Chui	20% (n-10)	50% (n-10)	-	40% (n-10)	20% (n-10)
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Besides the following factors were established upon review of out-patient medical cards:

- In 12,5% of cases parents of sick children refused from hospitalization and took treatment at home conditions and expedited report was sent without laboratory tests and decoding of etiological structure. These cases were diagnosed as “AEI of undefined etiology”.
- In 45% of cases antibiotics (ampicillin, cefazolin, cefanex and other) were prescribed for treatment of AEI patients at out-patient level without preliminary bacteriological tests;
- most often patients are referred to the in-patient level right away even if there are no indications for hospitalization;
- in terms of medical treatment one can observe non-compliance with clinical protocols on part of physicians and in many cases out-patients are prescribed to take antibiotics of cephalosporin range.

9.2. Review of clinical records with AEI diagnosis at in-patient level

In case of hospitalization to in-patient level the expedited report (form №058u) is submitted by medical worker from infectious department to the territorial CSSES, which is further to be included to the state statistical form №1.

In the framework of terms of reference there were examined 40 clinical stories at in-patient institutions located in regions covered by the survey. Also in order to review the situation in other regions of the Republic the research group requested for additional information from epidemiologists of CSSES of Talas City, Naryn City, Karakol City and Tokmok City in relation to management of AEI in-patients by infectionists.

The analysis of clinical records and the data received in the response to the request showed that:

- on average 25% of patients arrived to hospitalization have received antibacterial treatment at primary health care organizations;
- on average 20% patients arrived to the hospitalization have independently taken antibacterial drugs at home without prescription;
- only in 2 regions infection specialists prescribed to do testing for sensitivity to antibiotics: in Bishkek in 100% of cases physicians conducted detection of sensitivity and in Uzgen rayon in 10% of examined cases sensitivity to antibiotics was defined and in other surveyed regions sensitivity to antibiotics was not tested.

The analysis of received data shows that patients with diarrhea before they are hospitalized often take antimicrobial therapy either at FMC or independently at home without prescriptions, which obviously affects results of bacteriological drillability. The results of bacteriological tests of these patients show negative result on availability of

pathogenic microbe and correspondingly these patients are diagnosed as having AEI of undefined etiology.

It should be noted that in-patients with AEI diagnosis always do bacteriological testing. For example, in all examined cases (100%) samples were taken from in-patients for bacteriological tests to check presence of pathogenic microbe (Table 2).

Virologic tests were not prescribed and made in any examined case. It should be noted that there are no virologic laboratories in regions and are available only in Bishkek City and Osh City.

Table 2.

Management of AEI patients at in-patient level

Regions	Taking of antibacterial therapy before hospitalization to infectious department		Prescription of bacteriological examinations	Defining sensitivity of antibiotics
	At primary level	Independently		
Osh City	40% (n-10)	10% (n-10)	100% (n-10)	0% (n-10)
Uzgen rayon, Osh oblast	30% (n-10)	20% (n-10)	100% (n-10)	10% (n-10)
Bishkek City	10% (n-10)	30% (n-10)	100% (n-10)	100% (n-10)
Issyk-Ata rayon, Chui oblast	20% (n-10)	20% (n-10)	100% (n-10)	0% (n-10)
Talas City	20% (n-20)	20% (n-20)	100% (n-20)	0% (n-20)
Karakol City	20% (n-20)	30% (n-20)	100% (n-20)	0% (n-20)
Naryn City	10% (n-20)	20% (n-20)	100% (n-20)	0% (n-20)
Tokmok City	10% (n-20)	25% (n-20)	100% (n-20)	0% (n-20)

10. Activities of bacteriological laboratories

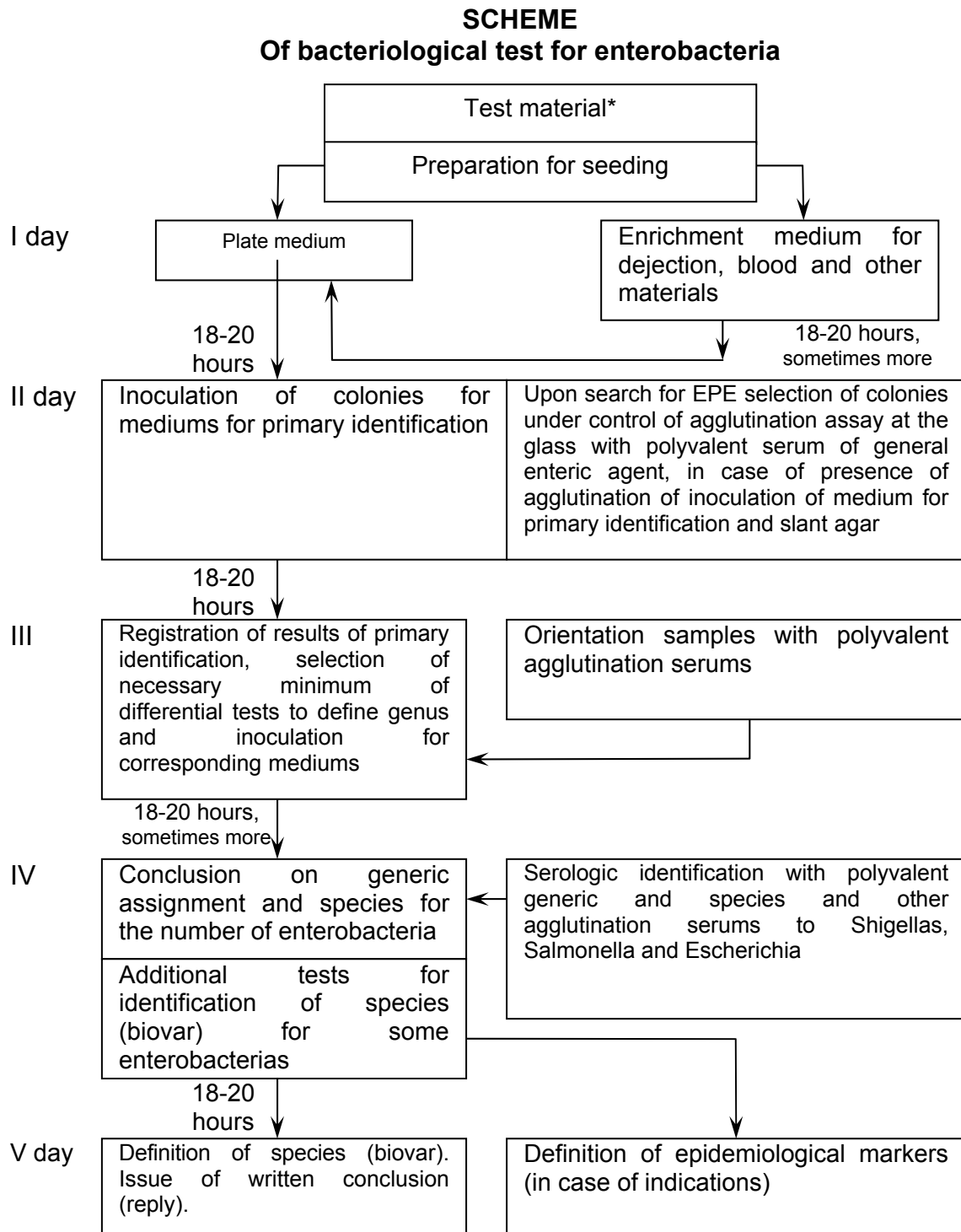
In the surveyed regions bacteriological laboratories are available only at Centers for SSES and territorial hospitals of Bishkek City, Osh City and Uzgen rayon of Osh oblast. The laboratories are structural units of treatment and prevention institutions of the Ministry of Health of the Kyrgyz Republic. All examined laboratories have permission issued by the Republican Certification Commission to function and to work with pathogenic biological agents. They are guided by existing legislation of the KR, organizations and methodological documents of the MoH of the KR. Laboratories conduct bacteriological tests, related to prevention and diagnostics of infectious disease and decode etiology of infectious diseases and conduct sanitary and bacteriological tests to define ways and factors of transmission of infection.

Delivery of materials from the patient with diarrhea to a laboratory is handled by medical personnel of the hospital with the special transport media. The very important

point for getting reliable and the most precise test results are appropriate and justified indications for bacteriological tests, timely and proper taking of samples from the patient by clinicians, which is also crucial for effectiveness of testing.

It should be noted that in accordance with the methodology of bacteriological testing results of tests for presence of pathogenic agent can be screened out only after 5 days and only in exceptional cases on the third day (Figure 10).

Figure 10

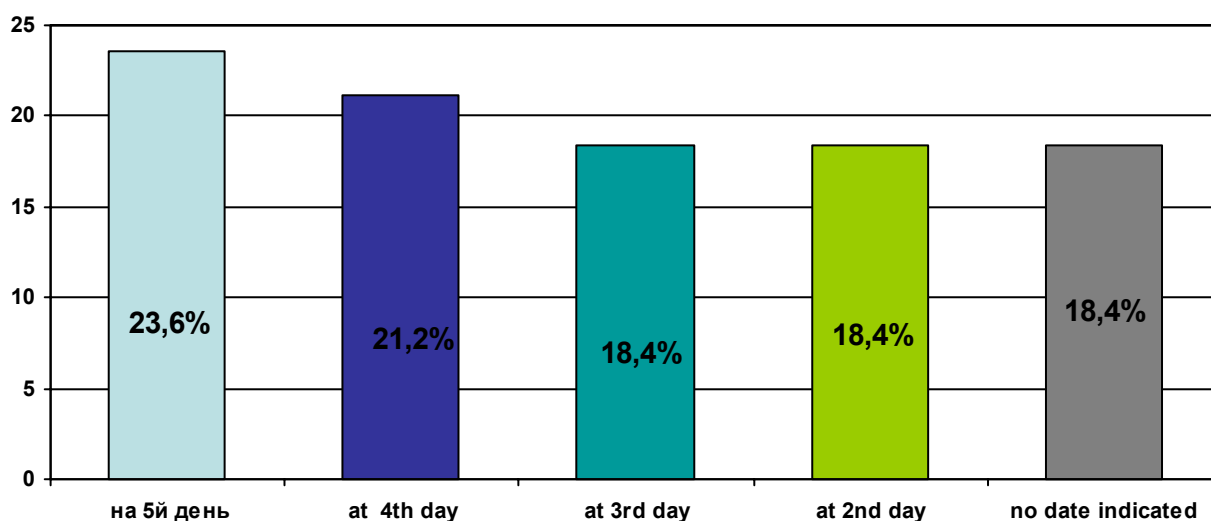


However, the conducted analysis indicates that only in 23,6% of examined cases test results were ready and issued on the fifth day and in 36,8% of cases results of bacteriological tests were ready and issued on the second and third days already (Figure 9). These facts show that most probably appropriate sequence of research methodology is not observed during bacteriological tests for existence of pathogenic microbes as a result of which drillability of etiological landscape is impossible. Besides, it was revealed during the research that in some institutions physiological solution is used instead of enrichment media as a basis of transport media for taking samples and bacteriological analysis. This also considerably affects reliability of results of bacteriological tests.

Figure 9

Timing for issuing results of etiological decoding of analysis of AEI patients

(n – 40)



Besides analysis of activities performed by laboratories in relation to the conduct of bacteriological tests and review of corresponding reporting forms showed that:

- quite often the work of bacteriologists is focused only to issue opportunistic microflora and attention is not paid to the search of other pathogenic agents and identification of microbe cultures is not always conducted by laboratories.
- test results are greatly affected by improper choice of the preserving agent during transportation and taking samples from patients for tests purposes.
- it was revealed during the research that some laboratories worked with expired diagnosticum and media (agglutination serum for salmonella typhimurium – from January 2008; Zonne – March 2008; Escherichia Coli - April, 2007).
- there is a lack of differentiated approach to testing as there were cases of unjustified bacteriological testing for enteric group of patients with other diagnosis.

11. Conclusion

Results of the research confirm that acute enteric infection of undefined etiology are the main problem of the health care system of the Kyrgyz Republic and it is necessary to improve the system in the field of efficient surveillance over these diseases.

- AEI of undefined etiology is the major problem of the health care system in the Kyrgyz Republic, making up 34% in the structure of infectious diseases;
- major reasons of bacteriological non-verifiability of AEI are administration of antibiotics without preliminary bacteriological testing;
- normative documents of the Ministry of Health do not have clear criteria to define cases that are subject to therapy by antibiotics, bacteriological testing and registration of patients who refused from hospitalization, treatment and examination of patients with acute enteric infections and for the purposes of epidemiological surveillance;
- upon prescription of antimicrobial therapy sensitivity of patients to this or that type antibiotics is practically not tested;
- improper choice of preserving agent used for transportation materials from AEI patient to a laboratory and taking samples has great impact on test results;
- culture of microbes is not identified and in 22,5% of cases test results are issued already on the second day;
- expiry dates of reagents and media are observed in laboratories;
- virological tests are not conducted to decode true etiological origin of AEI.

12. Recommendations

1. It is necessary to introduce further virological tests for patients with AEI of undefined etiology.
2. It is necessary to review and to improve the system of registration and reporting forms used by health care organizations for AEI records and treatment at out-patient level.
3. it is necessary to provide information for the population about risk factors of AEI and first symptoms of these diseases, as well as about importance of timely visit o the doctor.
4. To enhance laboratory services in terms of diagnostics and enlarging the volume of testing. It is necessary to expand the coverage of specialists by trainings and to conduct regular monitoring of the quality of laboratory tests and commitment of bacteriologists to observance of normative documents.
5. To increase capacity of health care organizations in relation to AEI diagnostics (training of specialists of laboratory services, introduction of rapid diagnostics to examine pollution of water and so on).
6. To review normative documents that regulate treatment of patients with AEI (orders of MoH, clinical protocols).

