Moldova TB Portal

1. Executive Summary

The rise of multidrug resistant tuberculosis (MDR-TB, defined as resistant to at least rifampicin and isoniazid) and extremely drug resistant tuberculosis (XDR, defined as resistant to rifampicin, isoniazid, any fluoroquinolone and to at least 1 of the following 3 drugs: capreomycin, kanamycin, and amikacin) is a severe threat to effective TB control as well as to successful treatment of individual patients. The concern that these strains could spread around the world further stresses the need for additional control measures, such as new diagnostic methods, better drugs for treatment, and a more effective vaccine. Patients harboring MDR strains of *Mycobacterium tuberculosis* (Mtb) need to be entered into alternative treatment regimens involving second-line drugs that are more costly, more toxic, and less effective. XDR-TB now constitutes an emerging threat for the control of the disease and the further spread of drug resistance, especially in HIV-infected patients [6, 7]. The World Health Organization (WHO) estimated that globally more than 500,000 TB patients are infected with MDR strains of Mtb [1-5].

The highest incidence of MDR-TB (about 20% of new and 60% of re-treatment cases) is reported in Eastern Europe for some of the countries of the former Soviet Union. To date there are no studies that have examined the genomic composition of *M. tuberculosis* isolates from the former Soviet Union.

The Republic of Moldova is high burden TB and MDRTB country. In 2012 the TB incidence was 160/100 000 population, which is the highest TB incidence in the European Region of the WHO. The prevalence of MDR-TB in the Republic of Moldova was 24% in new cases and 65% re-treatment cases in 2012 [6]. Reasons for the high TB and MDR-TB burden in the Republic of Moldova include poverty, lack of rapid diagnostic capacities and inconsistent availability of anti-TB drugs, especially for the treatment of MDR-TB [7]. Patients with TB, especially MDR-TB, are long-term hospitalized and hospitals are inadequately equipped with infection control measures to prevent nosocomial infection [8,9,10]. In the recent study was presents information regarding genotypic diversity of M.tuberculosis and predominance distribution of Beijing and H4(Ural) genotypes among MDRTB patients [11].

2. Justification

New hot spots of MDR-TB are documented every year [8]. Countries of the former Soviet Union have been among the most severely affected by this epidemic. The proportion of MDR in TB patients was the highest ever recorded worldwide [9]. Sequencing of genomes for MDR-TB and XDR-TB is essential, as the presence of expected sequence diversity in *M. tuberculosis* would provide a basis for understanding pathogenesis, immune mechanisms, and bacterial evolution. The bacterial factors that contribute to disease severity and type, in addition to host genetics, and the environment, remain still largely ill-defined. Understanding the mechanisms of drug resistance, virulence, spreading of Mtb, manifestation and clinical course of TB disease, based on a full genomic analysis is extremely important both for Moldova health programs and to support worldwide efforts to combat the disease.

Huge progress in TB research was made with the availability of the genomic sequence of the Mtb H37Rv type strain. Mtb H37Rv [10] was revealed to possess a sequence of 4,411,529 bp, the second largest microbial genome sequenced at that time. The characteristically high guanine plus cytosine (G+C content; 65.5%) was found to be uniform throughout most of the genome, confirming the hypothesis that horizontal gene transfer events are virtually absent in modern Mtb [11]. One of the most thoroughly studied characteristic of Mtb is the presence and distribution of insertion sequences (IS). Of particular interest is IS6110, which has been widely used for strain typing and molecular epidemiology due to its variation in insertion site and copy number [12]. It was determined that Mtb H37Rv codes for 3,924 ORFs, accounting for 91% of the coding capacity of the genome [11]. A bias in the overall orientation of genes with respect to the direction of replication was also found. On average, bacteria such as B.subtilis have 75% of their genes in the same orientation as that of the replication fork, while M. tuberculosis only has 59%. This finding led to the hypothesis that such a bias could be part of the slow-growing phenotype of the tubercle bacillus [13].

Genomic comparison has shown that gene content can vary between strains of M. tuberculosis. The analysis of complete genome sequences from clinical isolates identified that single nucleotide polymorphisms (SNPs), large sequence polymorphisms (LSPs), and regions of difference (RDs) originate from small deletions, deletions in homologous repetitive elements, point mutations, genome rearrangements, frame-shift mutations, and multi-copy genes [14, 15]. Fleischeman et al. suggested that genetic variation among Mtb strains might denote selective pressure and therefore might play an important role in bacterial pathogenesis and immunity [15].

Although associations between host and pathogen populations seem to be highly stable, the evolutionary, epidemiological, and clinical relevance of genomic deletions and regions of genetic variation remain ill-defined, as do the molecular basis of virulence and transmissibility [16].

Up to six Mtb lineages adapted to specific human populations were described by Gagneux et al. using comparative genomics and molecular genotyping tools: the Indo-Oceanic lineage, the East-Asian lineage, the East-African-Indian lineage, the Euro-American lineage, and two West-African lineages *[17].* One family of *Mtb* strains, Beijing, has attracted special attention. This hypervirulent family is reported to be common in several Asian studies and may possess selective advantages compared to other genotypes [18, 19]. This family is also more often associated with multi-drug resistance[20]. *Specific deletions associated with the hypervirulent Beijing/W strains of M. tuberculosis were identified [21].*

The genome of the *M. tuberculosis* laboratory strain H37Rv was completely sequenced (GenBank accession no. NC_000962) and compared to the complete genome sequence of *M. tuberculosis* strain CDC1551. (1,2). The circular representation of the *M. tuberculosis* chromosome illustrated in Fig.1 depicts the location of each predicted protein coding region as well as selected features differing between the CDC1551 and H37Rv strains, including large sequencing polymorphisms (LSPs) and single nucleotide polymorphisms (SNPs).

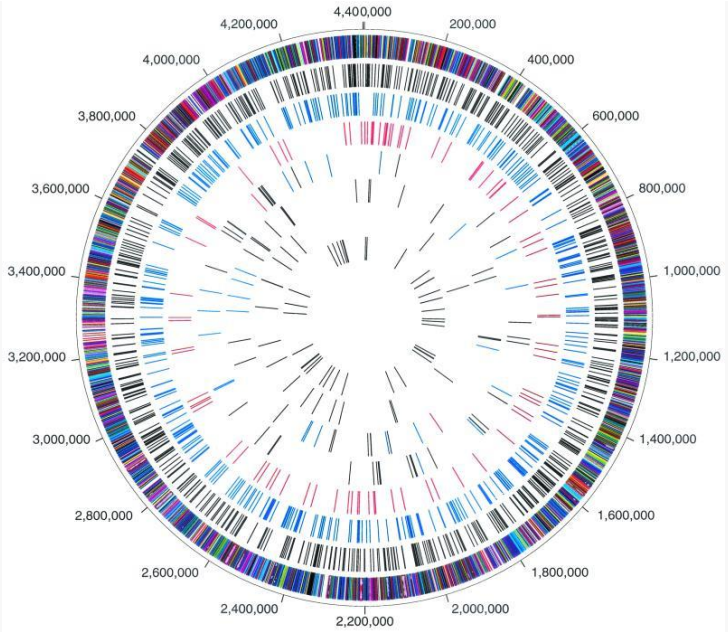

FIG.1.

Circular representation of the *M. tuberculosis* chromosome illustrating the location of each predicted protein-coding region as well as selected features differing between the CDC1551 and H37Rv strains. The outer concentric circle shows predicted protein-coding regions on both strands, color coded according to role category. The second concentric circle shows the location of nonsynonymous substitutions (black). The third concentric circle shows the location of synonymous substitutions (blue). The fourth concentric circle shows the location of substitutions in noncoding regions (red). The fifth concentric circle shows the location of insertions in strain CDC1551, including coding (black) and noncoding (blue) regions, and the location of phage phiRv1 (red). The sixth concentric circle shows the location of insertions in strain H37Rv, including coding (black) and noncoding (blue) regions, and the location of phage phiRv1 (red). The seventh concentric circle shows the location of IS*6110* insertion elements in strains CDC1551 (blue) and H37Rv (red). The eighth (innermost) concentric circle shows the location of tRNAs (blue) and rRNA (red).

The two genomes contained notable differences. The genetic variability in *M. tuberculosis* arises through a complex evolutionary process that involves recombination or multiple insertion-deletion events occurring independently at the same locus. The H37Rv strain contained 37 insertions (greater than 10 bp) relative to strain CDC1551. Twenty-six insertions affected open reading frames (ORFs) and 11 were intergenic. The insertions in strain H37Rv included tandem repeats, additions to the 5′ or 3′ ends of ORFs, and the addition of complete ORFs. Complete ORFs included three encoding hypothetical proteins (Rv0793, Rv3427c, Rv3428c), two encoding PPE proteins (Rv3425, Rv3426), one encoding a PE_PGRS protein (Rv3519), and two encoding proteins with putative functions (Rv0794c, a dihydrolipoamide dehydrogenase, and Rv0792c, a putative transcriptional regulator). Forty-nine insertions were identified in strain CDC1551 relative to strain H37Rv. Thirty-five insertions affected ORFs and 14 were intergenic.

The IS3-type insertion sequence IS*6110* is the principal epidemiological marker for *M. tuberculosis*. A number of the insertions and deletions were associated with this insertion sequence, suggesting a role for this element in genome plasticity [22, 23]. Studies have shown that homologous recombination between nearby copies of IS*6110* may result in genomic deletions and can be a mechanism for generating genomic diversity [24].

There are no studies that have examined the genomic composition of *M. tuberculosis* isolates from the high MDR- and XDR-TB burden countries (former Soviet Union Republics). The bacterial factors that contribute to disease severity and type, in addition to host genetics, and the

environment remain largely unknown. Understanding the mechanisms of drug resistance, virulence, spreading of Mtb, manifestation and clinical course of TB disease, based on a full genomic analysis is extremely important both for Moldova health programs and to support worldwide efforts to combat the disease.

The development of MDR- and XDR-TB is the result of a number of mutational events which lead to the formation of resistance to antituberculosis drugs. *During anti-TB treatment, Mycobacterium tuberculosis faces selective pressure of anti-TB drugs.* Resistance to TB drugs provides a significant benefit of Mtb for survival within the host. As a rule, the identification of drug resistance of *Mycobacterium tuberculosis* is carried out using phenotypic methods and an assumption regarding the presence or absence of specific mutations could be made on the basis of Mtb resistance or susceptibility to anti-TB drugs. Whole genome sequencing could detect possible mutational events (SNPs in important proteins, regulatory regions, rearrangements, duplications, etc.) in other genes of mutant drug resistant Mtb strains and reveal possible relationships between the spectrum of Mtb drug resistance and other characteristics of mycobacteria, for example, virulence. It is known that some Mtb families, in particular, Beijing, demonstrate significant drug resistance and high virulence. Nevertheless, the relationship of these two Mtb characteristics is not fully resolved for all known Mtb families, despite numerous experimental studies. Sequencing Mtb strains genomes could determine the possible correlation between drug resistance and features of genes involved in mycobacteria-host interaction. Genetic variation may have an important role in disease pathogenesis and immunity. Putative virulence genes identified by homology and sequence analysis will later be studied using classical bacterial pathogenesis techniques, e.g., gene knockout experiments, to determine their contribution to pathogenesis.

3. OBJECTIVES

We propose sequencing about 150 genomes of XDR-TB and MDR-TB from samples collected in Moldova in order to:

1. Reveal phylogenetic/phylogeographic peculiarities of Mtb strains in Moldova;
2. To establish the profiles of M. tuberculosis isolates genotypes and the importance of these in transmission of infection; to reveal the local characteristics of causative agent circulation throughout the country.

3. Further investigate differences between genomes of TB strains with varied resistance to drugs varied clinical manifestation of disease,;
4. Perform comparative analysis of MDR- and XDR-TB strains from Moldova with strains of *M. tuberculosis* H37Rv, *M. tuberculosis* CDC1551 and strains from other countries;
5. Add to the existing body of information and knowledge to promote research resulting in creating new generation of TB drugs, vaccines, and diagnostics.

The results of this work will be unique because:

6. Multiple XDR and MDR Mtb genomes from Moldova samples have never been sequenced before.
7. The availability of collected clinical metadata that describes patients' history will allow for the selection of strains from hundreds of samples, providing a unique opportunity to study the variability and dynamics of TB genome mutations.

4. ELIGIBILITY

To be eligible for study enrollment, individuals must meet all of the Inclusion Criteria and none of the Exclusion Criteria. HIV-positive individuals and HIV-negative individuals will be included in this study.

Inclusion criteria

Male and female New or Relapse TB patients of any ethnicity and race, both HIV negative and positive, are eligible for the study if they:

- have signed informed consent to specimen collection,
- are 18 years of age or older; **and**
- are known to be sputum smear-positive, based on prior examination of sputum; **and**
- have positive culture on liquid or solid media **and**
- have DST result by phenotypic or genotypic tests **and**
- are sensitive strain to all first line TB drugs, **or**
- are confirmed resistance to INH&RIF, **or**
- are confirmed resistance to INH&RIF and quinolone and one injectable drugs

The participant that meat inclusion criteria will be recruited to participate into the study and will be followed for the informed consent process. After submission of the informed consent, participants will be asked to provide at least 3 sputum specimens of min 3 ml in volume. The sputum will be tested on microscopy, GeneXpert MTB/RIF, MGIT, LJ culture.

Participants with pozitive MGIT, LJ culture will be retained into the sudy.

Exclusion Criteria

a) Patients are not eligible for the study if the quantity of respiratory secretions is not sufficient;

b) Subjects with only extra-pulmonary disease;

c) Subjects under 18 years of age;

d) Inability to provide informed consent (e.g. prisoners, mentally impaired subjects).

5. SUBJECT ENROLLMENT

Screening

Adult subjects meeting inclusion criteria will be asked to participate. Subjects will be recruited at outtpatient clinic settings and inpatient hospital settings. Individuals will be asked by clinic staff if they would be interested in participating in the study. Interested individuals will be referred to study personnel for informed consent procedure. Participants will be told that participation is voluntary and that they have the opportunity to ask questions individually. They will also be told that refusal to participate into the study will not affect their level of care. A consent form will be signed by all participants.

Participant Compensation

Participants will not receive aditional funds or compensation.

6. STUDY DESIGN AND PROCEDURES

This will be an one-center study to collect bacteriologically and clinically well-characterized materials of adult subjects with sensible and drug-resistant TB.

The protocol will be submitted to IRB for approval.

Sample Size

Enrollment will take place at one site – PPI Chisinau. Enrollment target is 150 eligible participants over 1 year. It is expected to enroll 30 TB patients with isolated *M.tuberculosis* strain sensitive to all first line drugs; and 120 TB patients with confirmed MDR; from these minimum 30 will be with XDRTB. The expected duration of subject participation is one to two days for each participant.

Enrollment/Baseline

After obtaining informed consent, for each patient will be completed the individuall CRF on paper and electronic verssion (see annex 1).

Specimen Collection

- Participants will be asked to provide 3 sputum specimens over 1 to 2 days. Each specimen should be at least 3 ml or greater in volume for diagnostic purposes and storage.
- On Day 1, each participant will be asked to submit one spot sputum (S1) after enrollment and a second spot sputum after at least 2 hours (S2). Whenever possible, participants will be asked to provide a third sputum (S3) either on the day of enrollment or the following day.

Specimen Flow and Characterization

At Collection Site

All three sputum will be gather toghether. They will be used for decontamination. Specimens will undergo the following:

- Smear microscopy
- Xpert MTB/RIF
- MGIT and LJ culture
- MTB species identification for the pozitive culture (on first positive culture – TBc Id (BD or SD) or MTBDRplus, MTBDRsl)
- 1st and 2nd line MGIT DST
- 1st and 2nd line LJ DST ???
- HIV testing
- CD4 count (optional)

The rest will be stored at 4°C max 5 days for backup.

Pozitive culture

From MGIT pozitive culture, after identification will be performed:

a) 1st line DST: (SIRE) and PZA

b) 2nd line DST: MGIT (OFL, LVX, MOX (0,5; 2,0 µg), AMK, CAP, ETH).

The bacterial suspension in medium H7 will be aliqoted in 4 cryovials and will be stored at -70°C till the shipment of Reference Laboratory. One aliqout will be apart o local bank and will not be shipped.

LJ slants from positive MGIT cultures (subculture) will be stored on-site laboratry for 6 months after the strain shipment.

Sample selection for shipment

Mtb strains should meet the following criteria for shipment to Reference Laboratory:

a) MTB identified

b) DST MGIT finalised for I and II line

c) HIV result available

d) Clinical information collected (comorbidities, AB usage, TB treatment etc.)

e) Xray and/or CT results available.

(All clinical and laboratory CRF should be completed).

At Reference Laboratory Broad

a) Whole genome sequencing (WGS). Sequencing data will be used to identify strains and to determine mixed infections.

b) Strain typing (i.e. MIRU, RFLP or spoligotyping)

7. Data analysis.

Our goal is to perform comparative analysis of all existing TB genomes, find SNPs and find correlations of genome variations with a) patients' medical history, and b) resistance of corresponding bacteria to known drugs. For annotation purposes, we will map sequenced reads to the *M. tuberculosis* reference genome (H37Rv). We will use filtered, high quality variants for genome-wide association study (GWAS) using the Efficient Mixed-Model Association (EMMA) and haplotype likelihood ratio (HLR) tests. We will look for variants with high association to the MDR and XDR phenotypes, as well as resistance to specific drugs using the clinical and *in vitro* data available for these samples. We will also look for evidence of genomic changes over time that appear to have given rise to stronger resistance to various drugs.

8. Data release policy.

All sequences generated under this proposal will be submitted to GenBank. Assembled contigs and scaffolds will be deposited in the Whole Genome Shotgun section of GenBank within 45 calendar days of completing the shotgun or high-throughput sequencing. If it is determined that the final assembly can be significantly improved, an updated record will be deposited in the appropriate part of Genbank when complete.

Also, we intend to make all genomic data and associated de-identified clinical metadata

public through the NIAID Bioinformatics Resource Center PATRIC (patricbrc.org).

Annotation data will be made available via GenBank and PATRIC BRC web sites. Annotation data will be released within 45 calendar days of being generated.

9. Literature cited.

1. Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance / Geneva, World Health Organization. – 1997. - Document WHO/TB/97.229.
2. Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Report 2: Prevalence and trends. / Geneva, World Health Organization. – 2000. - Document WHO/CDS/TB/2000.278.
3. Anti-tuberculosis drug resistance in the world: third global report. The WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance 1999–2002. / Geneva: WHO. - 2004. – Document WHO/HTM/TB/2004.343.
4. Cohn D, Bustreo F, Raviglione M. Drug resistance in tuberculosis: review of the worldwide situation and WHO/IUATLD global surveillance project / Clin. Infect. Dis. – 1997. – Vol. 24 (Suppl. 1). - S121–S130.
5. Espinal M et al. Global Trends in resistance to anti-tuberculosis drugs / New Engl. J. Med. – 2001. – Vol. 344. – P. 1294–1302.
6. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe. Stockholm, Sweden: European Centre for Disease Prevention and Control; 2013.
7. Jenkins HE, Plesca V, Ciobanu A, et al. Assessing spatial heterogeneity of multidrug-resistant tuberculosis in a high-burden country. Eur Respir J 2013: 42(5): 1291-1301.
8. World Health Organization. Joint tuberculosis control programme review mission to the Republic of Moldova. : WHO Regional Office for Europe. Copenhagen; 2012.
9. Jenkins HE, Ciobanu A, Plesca V, et al. Risk factors and timing of default from treatment for non-multidrug-resistant tuberculosis in Moldova. Int J Tuberc Lung Dis 2013: 17(3): 373-380.

10. Jenkins HE, Crudu V, Soltan V, Ciobanu A, Domente L, Cohen T. High risk and rapid appearance of multidrug resistance during tuberculosis treatment in Moldova. Eur Respir J 2014: 43(4): 1132-1141.
11. V.Crudu, S. Niemann, M.Merker, Ch.Lange, Elena Romancenco, Ecaterina Noroc, Sofia Alexandru, D. Chesov, A.Catanzaro. Beijing and H4/Ural genotypes of M.tuberculosis are predominating among MDRTB patients in Moldova. 45 IUATLD Conference, Barcelona, 2014. Poster discussion.
12. Extensively Drug-Resistant Tuberculosis / K. Dheda [et al.] // N. Engl. J. Med. – 2008. – Vol. 359, № 27. – P. 2390.
13. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006; 368: 1575-80.
14. Zignol M, van Gemert W, Falzon D, Sismanidis C, Glaziou P, Floyd K, Raviglione M. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007-2010. Bull World Health Organ 2012; 90:111-9.
15. Skrahina A, Zalutskaya A, Sahalchyk E, Astrauko A, van Gemert W, Hoffner S, Rusovich V, Zignol M. Alarming levels of drug-resistant tuberculosis in Moldova: results of a survey in Minsk. Eur Respir J 2011; Oct 20. [Epub ahead of print].
16. Cole ST, Saint Girons I. Bacterial genomics. FEMS Microbiol Rev 1994; 14: 139-60. 30. Cole ST, Brosch R, Parkhill J, et al. Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature 1998a; 393: 537-44.
17. Sreevatsan S, Pan X, Stockbauer KE, et al. Restricted structural gene polymorphism in the Mycobacterium tuberculosis complex indicates evolutionarily recent global dissemination. Proc NatlAcadSci U S A 1997; 94: 9869-74.
18. vanEmbden JD, Cave MD, Crawford JT, et al. Strain identification of Mycobacterium tuberculosis by DNA fingerprinting: recommendations for a standardized methodology. J ClinMicrobiol 1993; 31: 406-9.
19. Cole ST. Learning from the genome sequence of Mycobacterium tuberculosis H37Rv. FEBS Lett 1999; 452: 7-10.
20. Filliol I, Motiwala AS, Cavatore M, et al. Global phylogeny of Mycobacterium tuberculosis based on single nucleotide polymorphism (SNP) analysis: insights into tuberculosis evolution, phylogenetic accuracy of other DNA fingerprinting systems, and recommendations for a minimal standard SNP set. J Bacteriol 2006; 188: 759-72.

21. Fleischmann RD, Alland D, Eisen JA, et al. Whole-genome comparison of Mycobacterium tuberculosis clinical and laboratory strains. J Bacteriol 2002; 184: 5479-90.
22. Hirsh AE, Tsolaki AG, DeRiemer K, Feldman MW, Small PM. Stable association between strains of Mycobacterium tuberculosis and their human host populations. Proc NatlAcadSci U S A 2004; 101: 4871-6.
23. Gagneux S, DeRiemer K, Van T, et al. Variable host-pathogen compatibility in Mycobacterium tuberculosis. Proc NatlAcadSci U S A 2006; 103: 2869-73.
24. Glynn JR, Whiteley J, Bifani PJ, Kremer K, van Soolingen D (2002) Worldwide occurrence of Beijing/W strains of Mycobacterium tuberculosis: a systematic review. Emerg Infect Dis 8: 843–849.
25. Phyu S, Jureen R, Ti T, Dahle UR, Grewal HM (2003) Heterogeneity of Mycobacterium tuberculosis isolates in Yangon, Myanmar. J ClinMicrobiol 41: 4907–4908.
26. Lillebaek T, Andersen AB, Dirksen A, Glynn JR, Kremer K (2003) Mycobacterium tuberculosis Beijing genotype. Emerg Infect Dis 9: 1553–1557.
27. Tsolaki AG, Gagneux S, Pym AS, et al. Genomic deletions classify the Beijing/W strains as a distinct genetic lineage of Mycobacterium tuberculosis. J ClinMicrobiol 2005; 43: 3185-91.
28. **McHugh, T. D., and S. H. Gillespie.** 1998. Nonrandom association of the IS*6110* and Mycobacterium tuberculosis: implications for molecular epidemiological studies. J. Clin. Microbiol.36**:**1410-1413.
29. **Warren, R. M., S. L. Sampson, M. Richardson, G. D. Van Der Spuy, C. J. Lombard, T. C. Victor, and P. D. van Helden.** 2000. Mapping of IS*6110* flanking regions in clinical isolates of Mycobacterium tuberculosis demonstrates genome plasticity. Mol. Microbiol. 37**:**1405-1416.
30. **Fang, Z., C. Doig, D. T. Kenna, N. Smittipat, P. Palittapongarnpim, B. Watt, and K. J. Forbes.**1999. IS*6110*-mediated deletions of wild-type chromosomes of *Mycobacterium tuberculosis*. J. Bacteriol. 181**:**1014-1020.

	Project active or finished (LMM PPI)	
1.	**Project Number**	No.U01 AI077957-01. NIAID RFA-AI-08-001.
	Title of Project	**Rapid Tests for Drug Resistance to Detect Extensively Drug-Resistant Tuberculosis.**
	Sponsored by:	National Institute of Allergy and Infectious Diseases (NIAID).
	Awarded Organization	Global Consortium for Drug-resistance TB Diagnostic, University California, San Diego
	Principal Investigator:	Dr. Antonino Catanzaro
	Duration	08.2009-09.2014
	Total Cost	$3.000.000
	Sub-grantee/contractor:	Phthisiopneumology Institute, Microbiology&Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Valeriu Crudu, MD PhD
2.	**Project Number**	1DP2OD006663-01
	Title of Project	**Prevalence, risk factors and consequences of complex M. tuberculosis infections**
	Sponsored by:	National Institutes of Health
	Awarded Organization	Brigham and Women's Hospital
	Principal Investigator:	Dr. Ted Cohen
	Project Start Date:	01-Jan-20
	Project End Date:	31-AUG-2014
	Total Cost	$2,672,711
	Sub-grantee/contractor:	Phthisiopneumology Institute, Microbiology&Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Valeriu Crudu, MD PhD
3.	**Project Number**	223681
	Title of Project	**Clinical research on tuberculosis drug- resistance in Europe. Collaborative Project (Large-scale integrating project).**
	Sponsored by:	EC contribution FP7-HEALTH-2007-B
	Awarded Organization	PG12 – EU FP7/TB PAN-NET.
	Principal Investigator:	Christoph Lange
	Project Start Date:	1-JAN-2009
	Project End Date:	31-12-2013
	Total Cost	10,998,270 €
	Sub-grantee/contractor:	Phthisiopneumology Institute, Microbiology&Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Valeriu Crudu, MD PhD
4.	**Project Number**	No: 11.817.09.58A
	Title of Project	**The optimization of microbiological methods for rapid diagnostic and monitoring of MDRTB**
	Sponsored by: .	Financing by AS of RM
	Awarded Organization	Phthisiopneumology Institute
	Principal Investigator:	Valeriu Crudu, MD PhD
	Project Start Date:	01.01.2011
	Project End Date:	31.12.2014
	Total Cost	2374,9 thousand MDL
	Sub-grantee/contractor:	Phthisiopneumology Institute Microbiology&Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Valeriu Crudu, MD PhD
5.	**Project Number** .	No: 0100 MD 01660
	Title of Project	**Surveillance of anti-tuberculosis drug resistance in Moldova. 01.01.2005 – 31.12.2006**
	Sponsored by:	Financing by USAID
	Awarded Organization	Phthisiopneumology Institute
	Principal Investigator:	Valeriu Crudu, MD PhD
	Project Start Date:	01.01.2005
	Project End Date:	31.12.2006
	Total Cost	$215.000
	Sub-grantee/contractor:	Phthisiopneumology Institute Microbiology&Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Valeriu Crudu, MD PhD
6.	**Project Number**	No.T10/AG/02.
	Title of Project	**Surveillance of anti-tuberculosis drug resistance in republic of Moldova. 2011**
	Sponsored by:	Global Fund to Fight AIDS, Tuberculosis and Malaria Project in Moldova
	Awarded Organization	Phthisiopneumology Institute
	Principal Investigator:	Valeriu Crudu, MD PhD

	Project Start Date:	01.01.2011
	Project End Date:	31.04.2012
	Total Cost	$50.00
	Sub-grantee/contractor:	Phthisiopneumology Institute Microbiology&Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Valeriu Crudu, MD PhD
7.	**Project Number**	T10/AG/01_IFP
	Title of Project;	**Multidrug-Resistant Tuberculosis by analyzing genotypic Study of phenomenon of nosocomial transmission of diversity of DNA of M.tuberculosis strains**
	Sponsored by:	Global Fund to Fight AIDS, Tuberculosis and Malaria Project in Moldova
	Awarded Organization	Phthisiopneumology Institute
	Principal Investigator:	Valeriu Crudu, MD PhD
	Project Start Date:	01.01.2010
	Project End Date:	31.12.2012
	Total Cost	$75.00
	Sub-grantee/contractor:	Phthisiopneumology Institute Microbiology&Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Valeriu Crudu, MD PhD
8.	**Project Number**	T10-250-2013
	Title of Project	**Innovative model of outpatient MDR-TB case management in the context of rapid diagnostic implementation**
	Sponsored by:	Otsuka Farmaceutical Company
	Awarded Organization	Center PAS
	Principal Investigator:	Andrei Mosneaga, MD
	Project Start Date:	01.01.2012
	Project End Date:	31.12.2014
	Total Cost	$140.00
	Sub-grantee/contractor:	Phthisiopneumology Institute Microbiology&Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Valeriu Crudu, MD PhD
9.	**Project Number**	NCT01424670
	Title of Project;	**Safety and Efficacy Trial of Delamanid for 6 Months in Patients with MDRTB**
	Sponsored by:	Otsuka Pharmaceutical Company
	Awarded Organization	Phthisiopneumology Institute
	Principal Investigator:	Liliana Domente; MD
	Project Start Date:	01.01.2013
	Project End Date:	31.12.2014
	Total Cost	$300.00
	Sub-grantee/contractor:	Phthisiopneumology Institute Microbiology&Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Elena Romancenco, MD
10.	**Project Number**	T9-370-114
	Title of Project	**Enhancing TB diagnosis and MDR detection by rolling out Xpert MTB/RIF technology at district level, with special emphasis on high-risk groups – prisoners and PLWH.**
	Sponsored by:	Stop TB Partnership TB REACH
	Awarded Organization	Center PAS
	Principal Investigator:	Dr. Andrei Mosneaga
	Project Start Date:	01.01.2010
	Project End Date:	31.12.2012
	Total Cost	$ 1.400.000
	Sub-grantee/contractor:	Phthisiopneumology Institute Microbiology&Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Valeriu Crudu, MD PhD
11.	**Project Number**	5800
	Title of Project;	**Nano-encapsulation of anti-TB drugs for targeted delivery**
	Sponsored by:	Financing by Science and Technology Center in Ukraine (STCU)
	Awarded Organization	Academy of Science from Moldova,
	Principal Investigator:	Prof., Dr. Hab. Fliur Macaev
	Project Start Date:	01.01.2013
	Project End Date:	31.12.2014
	Total Cost	$19,528
	Sub-grantee/contractor:	Phthisiopneumology Institute Microbiology Morphology TB Laboratory, Chisinau, Moldova
	Project Director:	Valeriu Crudu, MD PhD
12.	**Project Number**	T11-12.2010

Title of Project;	**First Evaluation of an Improved Assay for Molecular Genetic Detection of Tuberculosis as Well as Rifampin and Isoniazid Resistances**
Sponsored by:	Hain Lifescience GmbH, Germany
Awarded Organization	Phthisiopneumology Institute, Microbiology&Morphology TB Laboratory, Chisinau, Moldova
Principal Investigator:	Valeriu Crudu, MD PhD
Project Start Date:	01.01.2010
Project End Date:	31.12.2011
Total Cost	$12,000

Recent Peer-reviewed Publications Microbilology&Morphology Laboratory PPI

1. Gunar Günther, Frank van Leth, Sofia Alexandru, Neus Altet, Korkut Avsar, Didi Bang, Raisa Barbuta, Graham Bothamley, Ana Ciobanu, Valeriu Crudu, Manfred Davilovits, Martin Dedicoat, Raquel Duarte, Gina Gualano, Heinke Kunst, Wiel de Lange, Vaira Leimane, Cecile Magis-Escurra, Anne-Marie McLaughlin, Inge Muylle, Veronika Polcová, Emanuele Pontali, Christina Popa, Rudolf Rumetshofer, Alena Skrahina, Varvara Solodovnikova, Victor Spinu, Simon Tiberi, Piret Viiklepp, Christoph Lange and TBNET. Multidrug-Resistant Tuberculosis in Europe, 2010–2011. Emerging infectious diseases. Volume 21, Number 3—March 2015
2. Matthias Merker, Camille Blin, Stefano Mona, Nicolas Duforet-Frebourg, Sophie Lecher, Eve Willery, Michael Blum, Sabine Rüsch-Gerdes, Lauren Cowan, James Posey, Igor Mokrousov, Valeriu Crudu, The Global Beijing Diversity Study Group, Philip Supply, Stefan Niemann & Thierry Wirth. Evolutionary history and global spread of the *Mycobacterium tuberculosis* Beijing lineage.Nature. Nature Genetic, 2015, January
3. Valafar F., Ramirez-Busby S.M., Torres J., Lynthia V. Paul, Rodwell T.C., Victor T.C., Rodrigues C., Gler M.T., Crudu V., Catanzaro T. Prognostic significance o f n ovel katG mutations in Mycobacterium tuberculosis. Int. J. Mycobacte riol. (2015), http://dx.doi.org/10.1016/j.ijmyco.2014.11.043
4. Christoph Lange, Ibrahim Abubakar, Jan-Willem C. Alffenaar, Graham Bothamley, Jose A. Caminero, Anna Cristina C. Carvalho,Kwok-Chiu Chang, Luigi Codecasa, Ana Correia, Valeriu Crudu, Peter Davies, Martin Dedicoat, Francis Drobniewski, Raquel Duarte, Cordula Ehlers, Connie Erkens, Delia Goletti, Gunar Gu¨nther, Elmira Ibraim, Beate Kampmann, Liga Kuksa, Wiel de Lange, Frank van Leth, Jan van Lunzen, Alberto Matteelli, Dick Menzies, Ignacio Monedero, Elvira Richter, Sabine Ru¨sch-Gerdes, Andreas Sandgren, Anna Scardigli, Alena Skrahina, Enrico Tortoli, Grigory Volchenkov, Dirk Wagner, Marieke J. van der Werf, Bhanu Williams, Wing-Wai Yew, Jean-Pierre Zellweger and Daniela Maria Cirillo for the TBNET. Management of patients with multidrugresistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement**.** ERJ Expres, March 2014; doi: 10.1183/09031936.00188313
5. Jenkins HE, Crudu V, Soltan V, Ciobanu A, Domente L, Cohen T. High risk and rapid appearance of multidrug resistance during tuberculosis treatment in Moldova. Eur Respir J. 2014 Feb 20.
6. J Torres, T Victor, T Rodwell, C Rodrigues, MT Gler, V Crudu, A Catanzaro, F Valafar. Novel katG Mutations Identified in INH-Resistance in Mycobacterium Tuberculosis Isolates. Journal of Clinical Microbiology, 2014, July
7. Rodwell TC, Valafar F, Douglas J, Qian L, Garfein RS, Chawla A, Torres J, Zadorozhny V, Soo Kim M, Hoshide M, Catanzaro D, Jackson L, Lin G, Desmond E, Rodrigues C, Eisenach K, Victor TC, Ismail N, Crudu V, Gle MT, Catanzaro A. Predicting Extensively Drug-resistant Tuberculosis (XDR-TB) Phenotypes with Genetic Mutations. J Clin Microbiol. 2014;52(3):781-9.
8. Naomi Hillery, MPH, Erik J. Groessl, PhD; Andre Trollip, PhD; Donald Catanzaro, PhD; Lynn Jackson, B.S.; Timothy C. Rodwell, MD, PhD, MPH Richard S. Garfein, PhD; S-Y Grace Lin, MS Kathleen Eisenach, PhD; Theodore G. Ganiats, MD; Daniel Park, MD; Camilla Rodrigues, MD; Valeriu Crudu, MD; Thomas C. Victor, PhD; Antonino Catanzaro. The Global Consortium for Drug-resistant Tuberculosis Diagnostics (GCDD): Design of a multi-site, head-to-head study of three rapid tests to detect extensively drug resistant tuberculosis. Nature, 2014 (submit)
9. Rebecca E. Colman, James M. Schupp, Nathan Hicks, David E. Smith, Jordan L. Buchhagen, Paul S. Keim, Faramarz Valafar, Valeriu Crudu, Lynn Jackson, Donald Catanzaro, Timothy C. Rodwell, Antonino Catanzaro, David M. Engelthaler. Detection of low-level mixed-population drug resistance in Mycobacterium tuberculosis using high fidelity amplicon sequencing. Nature, 2014
10. A P Trollip, D Moore, J Coronel, L Caviedes, S Klages, T Victor, E Romancenco, V Crudu, K Ajbani, V P Vineet, C Rodrigues, R L Jackson, K Eisenach, R S Garfein, T C Rodwell, E Desmond, E J Groessl, T G Ganiats, A Catanzaro. Second-line drug susceptibility breakpoints for Mycobacterium tuberculosis using the MODS assay. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease (Impact Factor: 2.61). 02/2014; 18(2):227-32. DOI: 10.5588/ijtld.13.0229

11. Jenkins HE, Ciobanu A, Plesca V, Crudu V, Galusca I, Soltan V, Cohen T. Risk factors and timing of default from treatment for non-multidrug-resistant tuberculosis in Moldova. Int J Tuberc Lung Dis. 2013 Mar; 17(3):373-80. doi: 10.5588/ijtld.12.0464.
12. Matt Hoshide, Lishi Qian, Camilla Rodrigues, Rob Warren, Tommie Victor,Henry B Evasco, Thelma Tupasi, Valeriu Crudu, James T Douglas. Geographical Differences Associated with SNPs in Nine Gene Targets among Resistant Clinical Isolates of Mycobacterium tuberculosis. University of Hawaii, Honolulu, Hawaii.Journal of clinical microbiology (Impact Factor: 4.16). 06/2013; DOI: 10.1128/JCM.00857-13
13. Fliur Macaev, Veaceslav Boldescu*, Valeriu Crudu, Serghei Pogrebnoi, Marina Zveaghinţeva, Eugenia Stingaci, Natalia Sucman, Vsevolod Pogrebnoi. Molecular concepts of macrophage targeting. Chem. J. Mold. 2013, 8(2), 21-31
14. Crudu V.; Stratan E.; Romancenco, E.; Moraru, N.; Turcan N, Domente L, Alexandru S, Niemann S, Rush-Gerdes S, Soltan V, Mosneaga A. Exogenous reinfection as a major risk factor associated with the spread of drug-resistant TB in hospitals from the country. Bulletin of the Academy of Science of Republic of Moldova, 4(36) 2012, Chisinau 2012, ISSN 1857-0011.
15. Crudu V.; Stratan E.; Romancenco, E.; Moraru, N.; Turcan N.; Allerheiligen V.; Hillemann A. The new version of molecular genetics methods for detection of tuberculosis and resistance to Rifampicin and Isoniazid. Bulletin of the Academy of Science of Republic of Moldova, 4(36) 2012, Chisinau 2012, ISSN 1857-0011.
16. Jenkins HE, Plesca V, Ciobanu A, Crudu V, Galusca I, Soltan V, Serbulenco A, Zignol M, Dadu A, Dara M, Cohen T. Assessing spatial heterogeneity of multidrug-resistant tuberculosis in a high-burden country.Eur Respir J. 2013 Nov; 42(5):1291-301. doi: 10.1183/09031936.00111812. Epub 2012 Oct 25.
17. Crudu V.; Stratan E.; Romancenco, E.; Moraru, N.; Turcan N.; Allerheiligen V.; Hillemann A. First Evaluation of an Improved Assay for Molecular Genetic Detection of Tuberculosis as Well as Rifampin and Isoniazid Resistances. Journal of Clinical Microbiology. 2012, v. 50, nr. 4, 1264–1269. ISSN: 0095-1137.
18. Crudu V, Romancenco E, Stratan E, Turcan N, Moraru N, Lesan V, Carchilan L. Study of phenomenon of nosocomial transmission of MDR TB by analyzing genotypic diversity of DNA of *M.tuberculosis* strains. Bulletin of the Academy of Science of Republic of Moldova , 4(32) 2011, ISSN 1857-0011
19. Cotelea T., Moruşciag L., Nițulescu G., Chiriţa I., Crudu V., Moraru N., E. Stratan, N. Turcan, E.Romancenco. The studying of antituberculosis activity of new synthesized compounds of Tioureide Acid 2-(2 – Pheniletil)-Benzoic. Bulletin of the Academy of Science of Republic of Moldova , 4(32) 2011, p. 127-130. ISSN 1857-0011.
20. Soltan V., Nalivaico N., Iavorschi C., Sain D., Serbulenco A., Crudu V., Burinschi V., Petrica V.. Situaţia epidemiologică şi realizarea Programului Naţional de Control şi Profilaxie a Tuberculozei pentru anii 2006-2010 în Republica Moldova. Buletinul Academiei de Ştiinţe a Moldovei Ştiinţe Medicale Revistă Ştiinţifico-Practică. 4(32)/2011; p.10-15.
21. Sain D., Crudu V., Râvneac L., Haidarlî I., Crivenco G., Jurja L., Tudos T., Moraru N., Ţîmbalari V. , Ciobanu S., Maruşceac I., Nepoliuc L., Aspecte de management al diagnosticului microbiologic şi tratamentului tuberculozei multidrogrezistente. Buletinul Academiei de Ştiinţe a Moldovei Ştiinţe Medicale Revistă Ştiinţifico-Practică. 4(32)/2011; p.27-31.
22. Crudu V., Domente L., Alexandru S., Ciobanu A., Romancenco E., Noroc E., Soltan V., Mosneaga A., Chesov D., Iavorschi C. Trend in TB control in Republic of Moldova: High MDRTB burden country. ERS, Annual Congress, Munich, 2014. Abstract Number: 1431, p.12.
23. Chesov D., Lange C., Daduna F., V. Crudu, R. Preyer, M. Ernst, B. Kalsdorf. Additional analysis of antigen-specific Interleukin-2 Release does not improve the performance of IGRAs for the differentiation of different states of mycobacterium tuberculosis infection. ERS, Annual Congress, Munich, 2014. Abstract Number: 3253.
24. Valeriu Crudu; Viorel Soltan, Andrei Mecineanu; Ana Ciobanu. A mobile phone intervention for improved TB control. ERS, Annual Congress, Munich, 2014. Presentation. ERS/WHO Joint Hot Topic "Tuberculosis (TB), tobacco and mobile phones" session.
25. Rodwell TC, Valafar F, Garfein RS, Douglas J, Rodrigues C, Crudu V, Victor TC, Gler M, Catanzaro A. Predicting XDR-TB Phenotypes Accurately with Single Nucleotide Polymorphisms. 17th Annual Conference: International Union Against Tuberculosis and Lung Disease – North America Region; February 28 - March 2, 2013; Vancouver, BC, Canada. 2013.
26. Crudu V, Romancenco E, Noroc E, Turcan N, Domente L, Alexandru S, Chesov D, Niemann S, Merker M, Rüsch-Gerdes S, Catanzaro A. Multidrug-resistant tuberculosis with mixed strains: a challenge in diagnostic and treatment of patients. The 34th annual meeting of the European Society of Mycobacteriology; June 30-July 3, 2013; Florence, Italy. 2013. P 256, p. 95.
27. Catanzaro A., R. Garfein, C. Rodrigues, T. Victor, K. Ajbani, E. Romancenco, E.Noroc, C. Hayes, A. Trollip, R. Jackson, T. Rodwell, V. Crudu. Rapid testing for drug susceptibility. ERS, Annual Congress, Barcelona, 2013. Abstract Number: 7257
28. Crudu V., Romancenco E., Noroc E., Turcan N., Carchilan L, Lesan V. Multidrug-resistant and extensively drug resistance tuberculosis has a strong public health and economic impact in the Republic of Moldova. ERS, Annual Congress, Barcelona, 2013. P1616; Abstract Number: 4240

29. Crudu V., E. Romancenco, E. Noroc, N. Turcan, Carchilan L, Lesan V. The MTBDRplus 2.0 for rapid diagnosis of multidrug-resistant tuberculosis among patients with high risk of TB Resistance. ERS, Annual Congress, Barcelona, 2013. P2779; Abstract Number: 3067
30. Catanzaro A, Rodwell T., Rodrigues C., Crudu V, Victor T., Ajbani K., Romancenco E., E.Noroc, Trollip A., Cindy Hayes, Roberta Lynn Jackson, Catanzaro A.,Theodore Ganiats, Groessl , Garfein R. Rapid testing for drug susceptibility. The 34th annual meeting of the European Society of Mycobacteriology. Florence, 2013. (op 212), p. 49
31. Crudu V., Romancenco E., Noroc E., Turcanu N., Domente L., Alexandru S. Emergence of XDR in high burden MDRTB country: a threat to public health and TB control program. The 34th annual meeting of the European Society of Mycobacteriology. Florence, 2013. (op 244), p. 52.
32. Crudu V., Romancenco E., Noroc E., Turcanu N. Rapid diagnosis of multi- and extensively drug resistant tuberculosis among patients with high risk of TB resistance. The 34th annual meeting of the European Society of Mycobacteriology. Florence, 2013. P 180, p. 91
33. Mosneaga A., Domente L, Alexandru S, Romancenco E., E.Noroc, Soltan V., Crudu V. Uptake of new TB diagnostics and diagnostic algorithms in the Republic of Moldova. 44 IUATLD Conference, Paris, 2013. S6, p. 10.
34. Rodwell TC, Valafar F, Garfein RS, Douglas J, Rodrigues C, Victor TC, Crudu V, Catanzaro T. Sensitivity and Specificity of Mutations for Predicting Global XDR-TB Phenotypes. 44 IUATLD Conference, Paris, 2013. S17, p. 21.
35. Valafar F, Rodwell TC, Garfein RS, Douglas J, Rodrigues C, Victor TC, Crudu V, Catanzaro T. Clinical molecular diversity of TB on a genome-wide scale: lessons learnt for molecular diagnostics. 44 IUATLD Conference, Paris, 2013. S17, p. 21
36. Helen E. Jenkins, V. Crudu, V.Soltan, A. Ciobanu, L. Domente, T. Cohen. Prevalence, timing of and risk factors for the appearance of multidrug-resistance during tuberculosis treatment. 44 IUATLD Conference, Paris, 2013. S500, p. 504
37. Antonino Catanzaro, Richard Garfein, Camilla Rodrigues, Thomnas Victor, Kanchan Ajbani, Elena Romancenco, Cindy Hayes, Andre Trollip, Roberta Jackson, Timothy Rodwell, Valeriu Crudu. Rapid testing for drug susceptibility. 44 IUATLD Conference, Paris, 2013.
38. Crudu V, Domente L, Alexandru S, Romancenco E, Vilc V. Noroc E, Turcan N., Soltan V, Mosneaga A. The burden of TB drug-resistance in Eastern Europe: the Moldavian experience. 44 IUATLD Conference, Paris, 2013. S4, p. 44.
39. Crudu V., Romancenco E., Noroc E., Turcanu N., Domente L., Alexandru S. Chesov D., Niemann S., Merker M., Sabine Rüsch-Gerdes, Antonino Catanzaro. MDR TB with mixed strains: a challenge in diagnostic and treatment of patients. INSPIR, Iasi, 2013.
40. Crudu V., Romancenco E., Noroc E., Turcanu N, Carchilan L, Lesan V. Noi posibilitati in diagnosticul rapid al tuberculozei multirezistente. SRP, Conferința "Patologia respiratorie în practica medicală curentă", 25-27.04.2013, Târgu-Jiu, Romania. P. 12
41. Crudu V.; Stratan E.; Romancenco, E.; Moraru, N.; Turcan N. New tools for rapid diagnosis of MDR TB. Societatea Română de Pneumologie. Conferința Secțiunii de Tuberculoză, ed.1. 27-29.09.2012, Timişoara. Volum Rezumate, pag.29
42. Crudu V., V. Botnaru , Golisceva O., Carchilan L. , Moraru N., Lesan V, Soltan V. Increasing TB drug resistance in Moldova during the 2006-2010. European Respiratory Journal; Volume 38, Supplement 55, 2011, p.46
43. Aspecte de management al diagnosticului microbiologic şi tratamentului tuberculozei multidrogrezistente / D. Sain, V. Crudu, L. Râvneac, I. Haidarlî, G. Crivenco, L. Jurja, T. Tudos, N. Moraru, V. Ŝâmbalari, S. Ciobanu, I. Maruşceac, L. Nepoliuc, A. Maximenco // Bul. Acad. de Ştiinţe a Moldovei. Ştiinţe medicale. – 2011. – Nr 4: Materialele Conferinţei Internaţionale INSPIR, Iaşi-Chişinău, 14-16 oct. 2011. – P. 27-31. – ISSN 1857-0011. – (Cat. C).
44. V. Soltan, N. Nalivaico, C. Iavorschi, D. Sain, A.Serbulenco, V. Crudu, V. Burinschi, V. Petrica. Situaţia epidemiologică şi realizarea Programului Naţional de Control şi Profilaxie a Tuberculozei pentru anii 2006-2010 în Republica Moldova // Bul. Acad. de Ştiinŝe a Moldovei. Ştiinŝe medicale. 2011. – Nr 4 : Materialele Conferinţei Internaţionale INSPIR, Iaşi-Chişinău, 14-16 oct. 2011. – P. 115.ISSN 1857-0011. – (Cat. C).
45. Crudu V., Golisceva O., Carchilan L., Moraru N., Leşan V., Soltan V. High prevalence of drug-resistant tuberculosis in Republic of Moldova, 1995-2009. ERS, vol. 36, supliment 54, September 2010, p.919.
46. Crudu V., Sabine RUCH-GERDES, Stefan Niemann, Blagodeteleva G., Ecaterina Stratan, Carchilan L., Moraru N., Leşan V. Poor infection control increase risk of reinfection with MDR or XDR-TB strains. ERS, vol. 36, supliment 54, September 2010, p.32
47. Crudu V., Soltan V., Carchilan L., Lesan V., Blagodeteleva G., Stratan E. Trends of primary drug resistance in Republic of Moldova, ERS, vol. 36, supplement 54, September 2010, p. 131
48. Crudu V., Rüsch-GerdeS S., Niemann S., Moraru N., Carchilan L., Leşan V., Stratan E., Soltan V. Failure of tuberculosis therapy by nosocomial transmission of multidrug resistant M.tuberculosis strains in a high incidence setting. Int J Tuberc Lung Dis., Volume 14, Number 11, supplement 3, November 2010, p. 569

49. Crudu V., Sabine Ruch-Gerdes, Stefan Niemann, Blagodeteleva G., Ecaterina Stratan, Carchilan L., Moraru N., Leşan V. Nosocomial transmission of multidrug-resistant M. tuberculosis strains in a high-incidence setting. Int J Tuberc Lung Dis., Volume 15, Number 11, supplement 3, November 2010, p.353
50. Crudu v., Soltan V., Moraru N., Golisceva O., Carchilan L., Leşan V., Stratan E., Buga A. Trends of primary drug resistance in Republic of Moldova. Int J Tuberc Lung Dis., Volume 14, Number 11, supplement 3, November 2010, p.235.
51. Crudu V., S Rüsch-Gerdes, S.Niemann, V Soltan, N.Moraru, V.Lesan, E Stratan, L Carchilan, G. Blagodeteleva. Assessment of the Nosocomial Transmission of MDR TB in Moldova using DNA fingerprinting of M.tuberculosis. Am J Respir Crit Care Med 181;2010:A4757