Child
& Adolescent
TB Working Group

Use of new drugs for children with DR-TB

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CONCISE CLINICAL REVIEW

New and Repurposed Drugs for Pediatric Multidrug-Resistant Tuberculosis

Practice-based Recommendations

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Abstract

It is estimated that 33,000 children develop multidrug-resistant tuberculosis (MDR-TB) each year. In spite of these numbers, children and adolescents have limited access to the new and repurposed MDR-TB drugs. There is also little clinical guidance for the use of these drugs and for the shorter MDR-TB regimen in the pediatric population. This is despite the fact that these drugs and regimens are associated with improved interim outcomes and acceptable safety profiles in adults. This review fills a gap in the pediatric MDR-TB literature by providing practice-based recommendations for the use of the new (delamanid and bedaquiline) and repurposed (linezolid and clofazimine) MDR-TB drugs and the new shorter MDR-TB regimen in children and adolescents.

Keywords: multidrug-resistant tuberculosis; *Mycobacterium tuberculosis*; child; adolescent; pediatric

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• www.cdc.gov/eid •

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Off-Label Use of Bedaquiline in Children and Adolescents with Multidrug-Resistant Tuberculosis

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We describe 27 children and adolescents <18 years of age who received bedaquiline during treatment for multidrug-resistant tuberculosis. We report good treatment responses and no cessation attributable to adverse effects. Bedaquiline could be considered for use with this age group for multidrug-resistant tuberculosis when treatment options are limited.

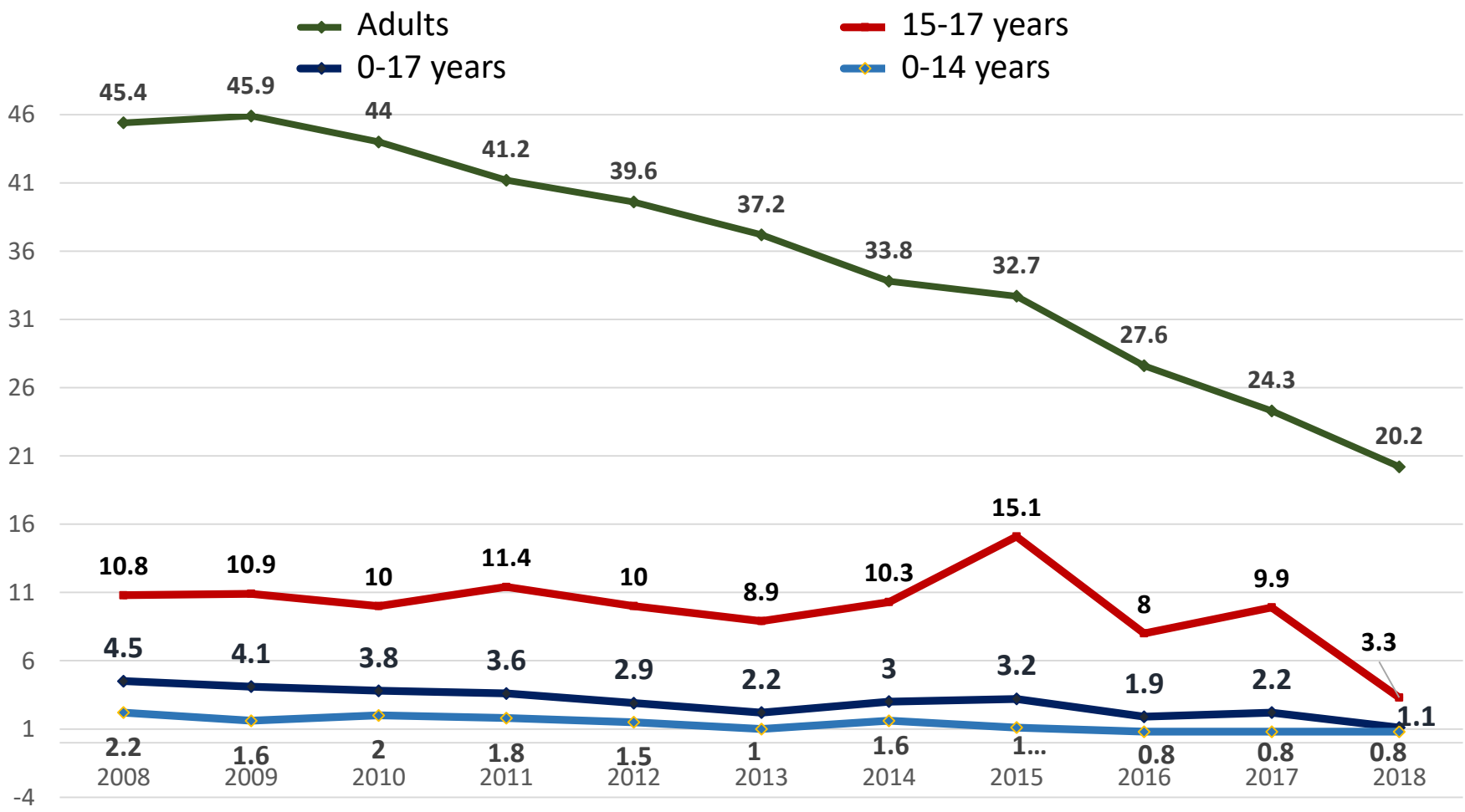
establishing laboratory diagnoses continue to lead to inappropriate management of disease among many children. Second, adverse effects from MDR TB treatments are common; in 1 cohort, >25% of children receiving an injectable drug suffered hearing loss (*5*). Third, for children and adolescents infected with more extensively resistant strains, treatment options are limited.

In 2013, following US Food and Drug Administration approval of bedaquiline (in 2012), the WHO released interim guidance on the use of this drug (*6*). Key determinants of eligibility to receive bedaquiline included the inability to construct an effective 4-drug regimen using other available

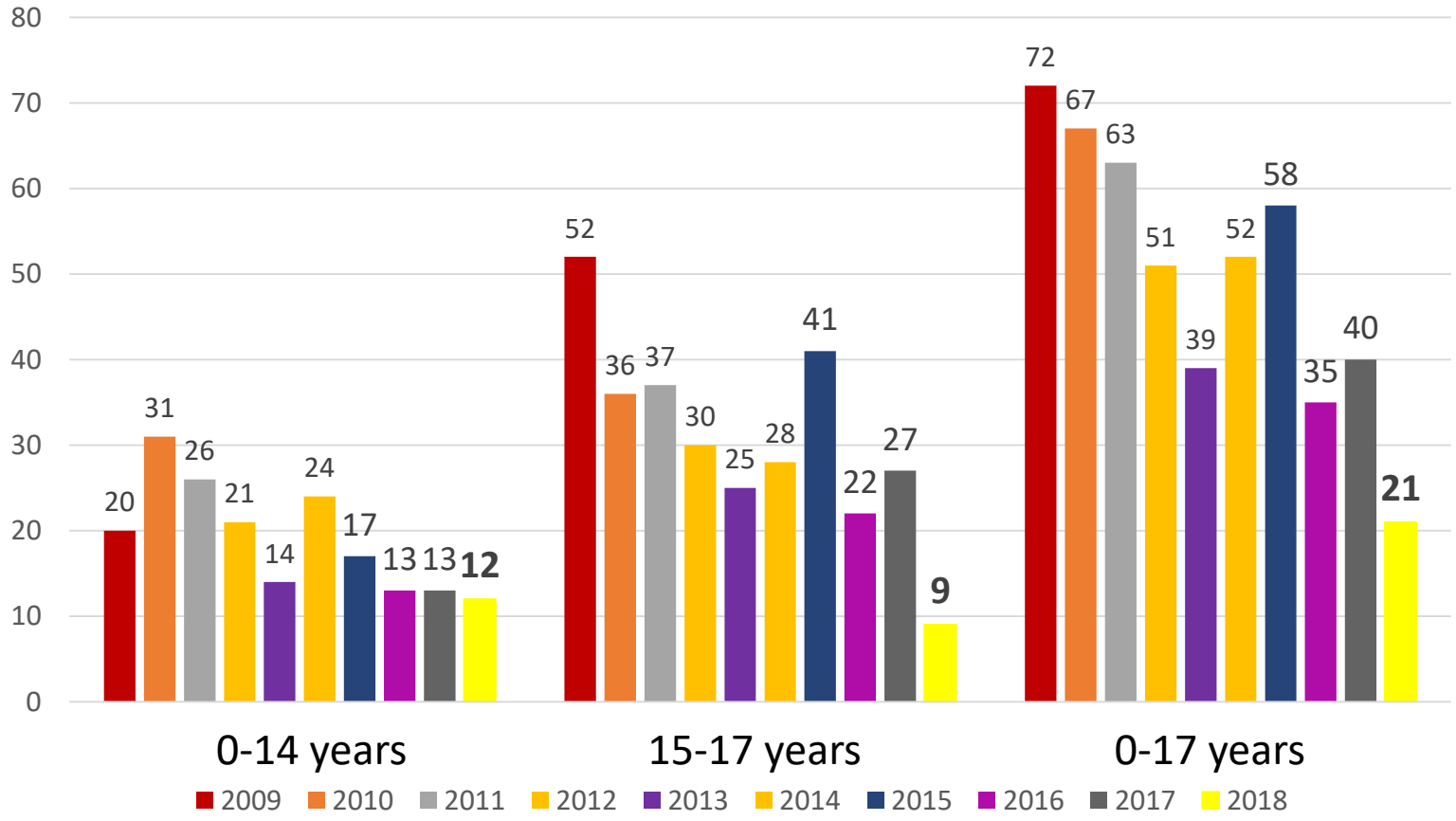
Table. Demographic, treatment, and outcome characteristics of a cohort of 27 children <18 years of age receiving bedaquiline for the treatment of MDR TB*

Characteristic	No. (%)
Country	
Belarus	15 (56)
South Africa	3 (11)
Tajikistan	6 (22)
Uzbekistan	3 (11)
Age, y, median (range)	16 (10–17)
Sex	
Female	15 (56)
Male	12 (44)
Weight, kg, median (range)	50 (35–76)
Body mass index, kg/m^2, median (IQR)	18.5 (17.2–19.6)
Cavities on baseline chest radiograph, n = 24	9 (38)
Baseline sputum smear positive	19 (70)
Baseline sputum culture positive	17 (63)
Baseline drug resistance pattern	
MDR TB	0 (0)
Pre–XDR TB	
Resistant to second-line injectable	3 (11)
Resistant to fluoroquinolone	6 (22)
XDR TB	18 (67)
Resistant drugs,† median (IQR), n = 24	5 (5–6)
Drugs in initial treatment regimen, median (IQR)	6 (6–7)
Drugs included in treatment regimen	
Moxifloxacin	6 (22)
Clofazimine	26 (96)
Linezolid	26 (96)
Imipenem	4 (15)
Bedaquiline treatment duration if completed, d, median (IQR), n = 20	172 (168–178)
Sputum culture negative at February 24, 2017, n = 23	23 (100)
Sputum culture negative after 24 wks of bedaquiline, n = 22‡	22 (100)
Reported adverse effects	
No grade 3 or 4	19 (70)
Grade 3 or 4, not caused by bedaquiline	3 (11)
Grade 3 or 4, caused by bedaquiline	5 (19)§

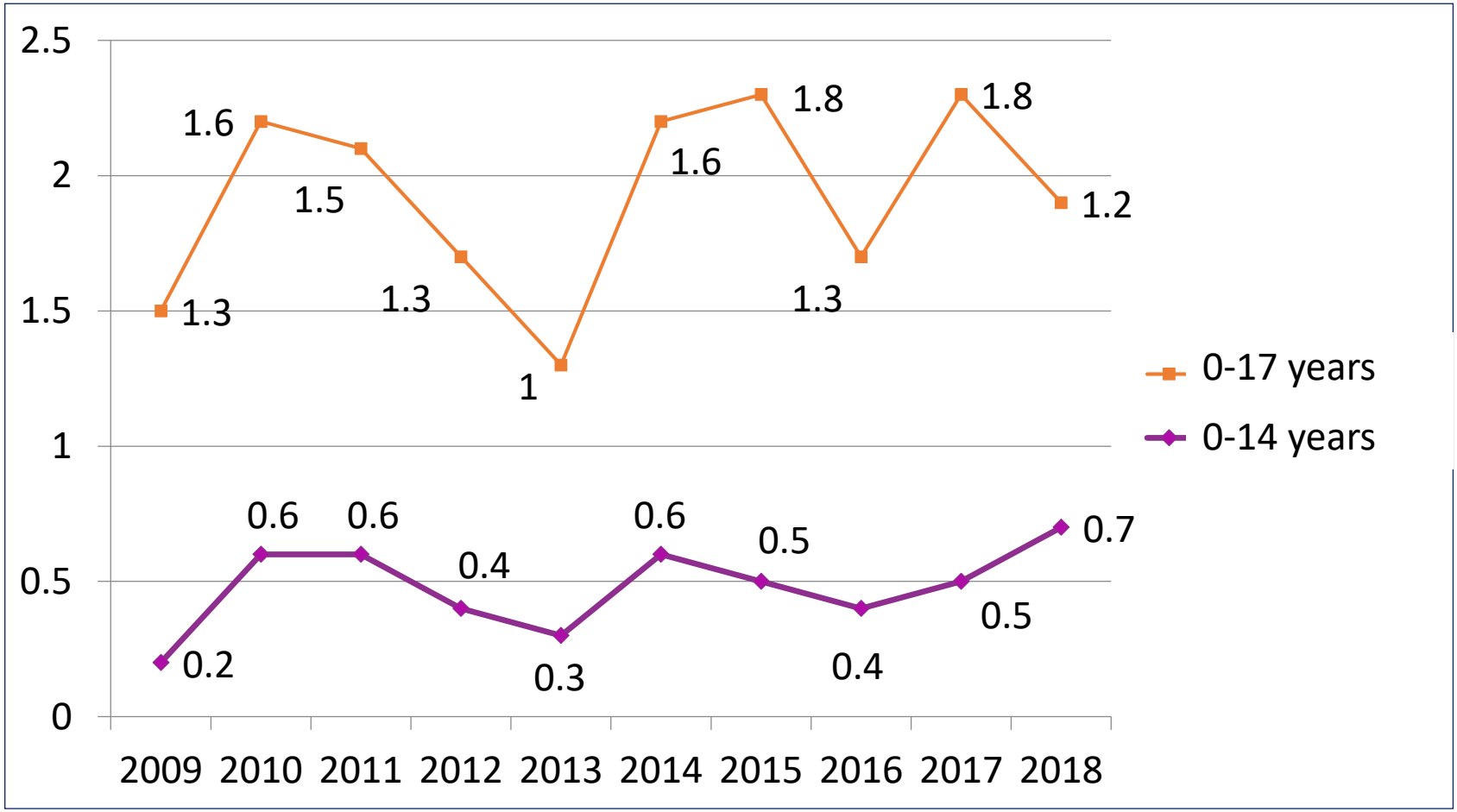
Belarus TB incidence (/100 000)



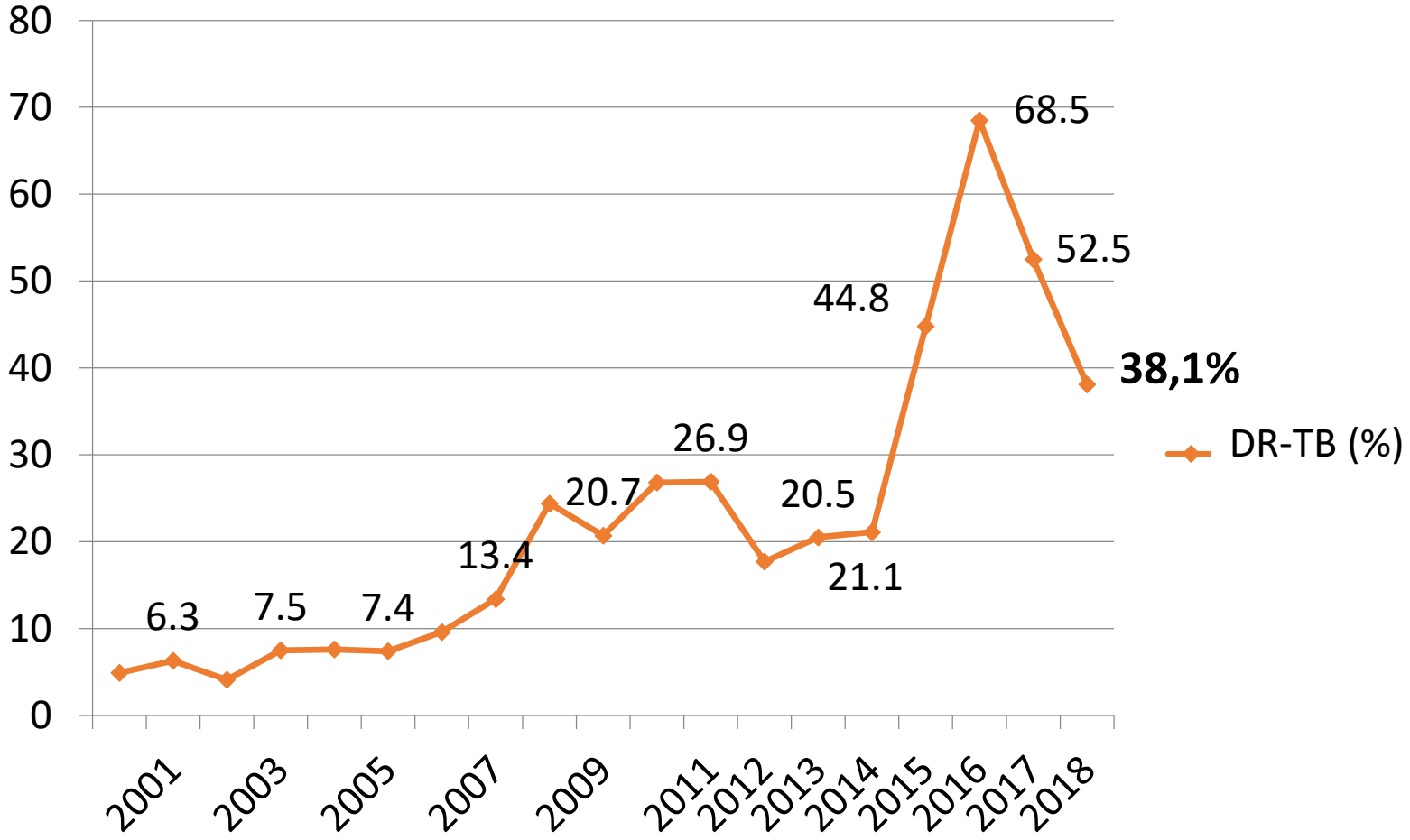
Belarus absolute number of child and adolescent TB cases



Belarus Child and adolescent TB Proportion (%) of all TB cases



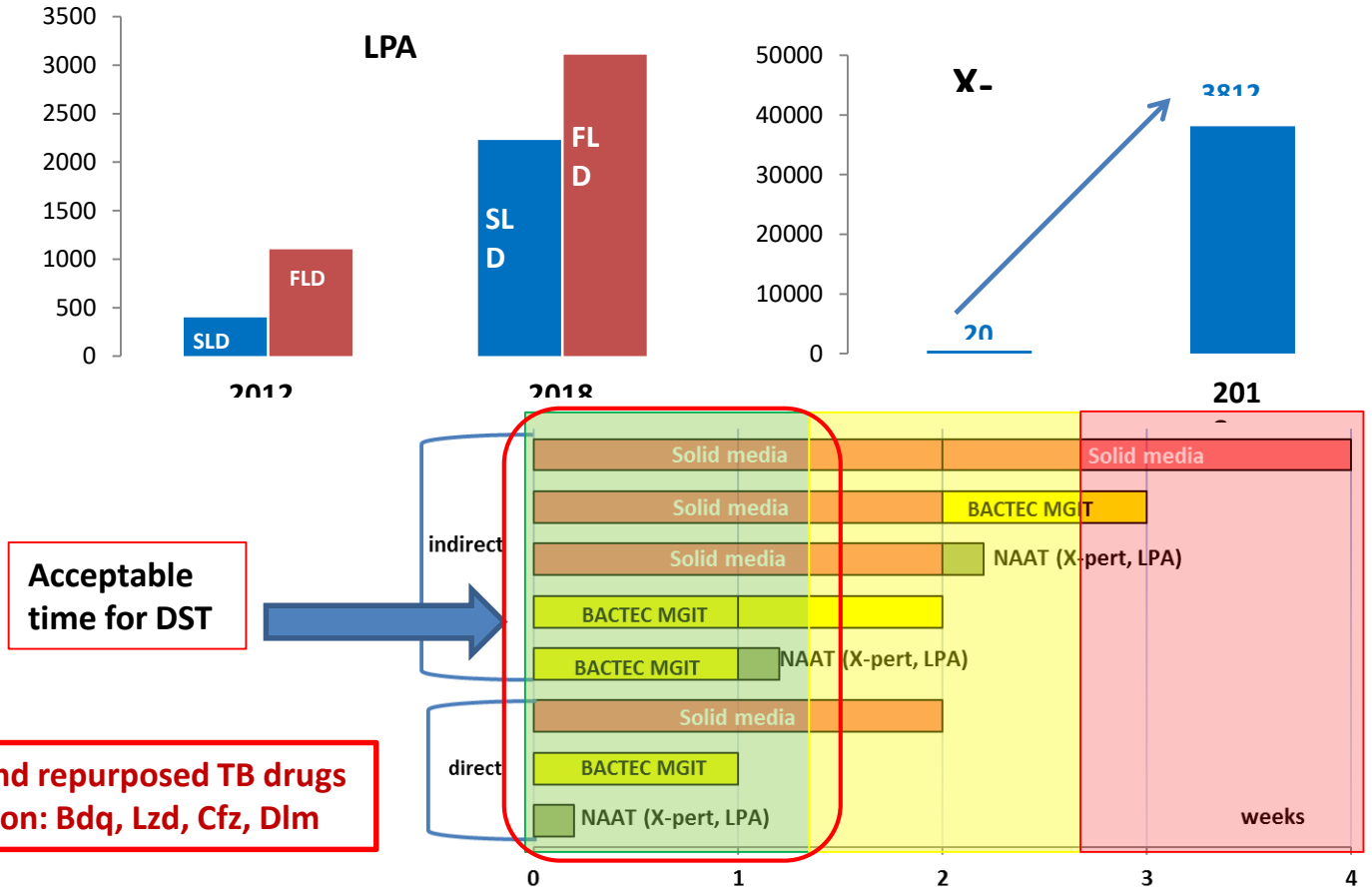
Belarus DR-TB proportion (%) in child and adolescent TB



MDR-TB Consilium

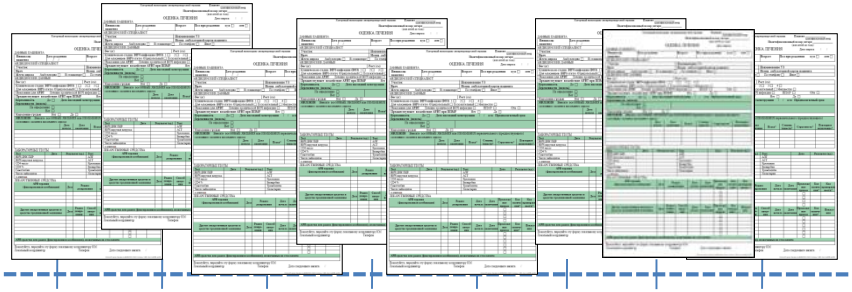
- Careful patient selection
- Designing treatment regimen in line with WHO recommendations
- Management of co-morbidities (e.g. HIV, DM)
- Treatment monitoring
- Active Drug Safety Monitoring and Management of Adverse Events (aDSM)
- Adherence issues
  - DOT, VOT
  - Alcohol and drug abuse
  - Mental health problems
  - Social support issues

Full scale-up of rapid molecular diagnostics

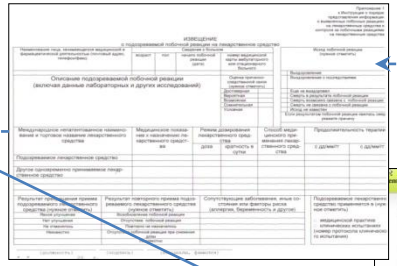


DST to new and repurposed TB drugs implementation: Bdq, Lzd, Cfz, Dlm

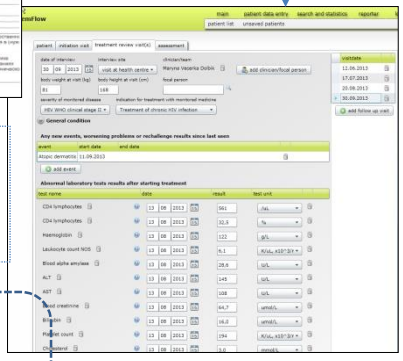
Active TB drug safety monitoring and management (aDSM)

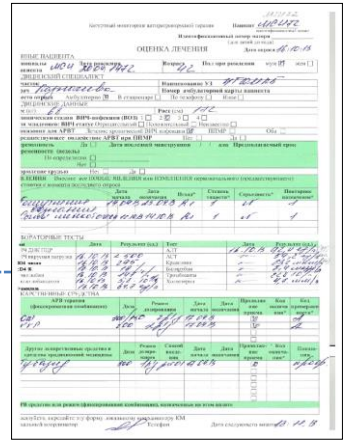


1 m | 2 m | 3 m | 4 m | 5 m | 6 m | 9m | 12 m | 15 m | 18 m | 21, 24 m



Data analysis and database input





Vigibase National database of ADR

National TB register

Analysis Report Recommendations

New TB drugs in children and adolescent

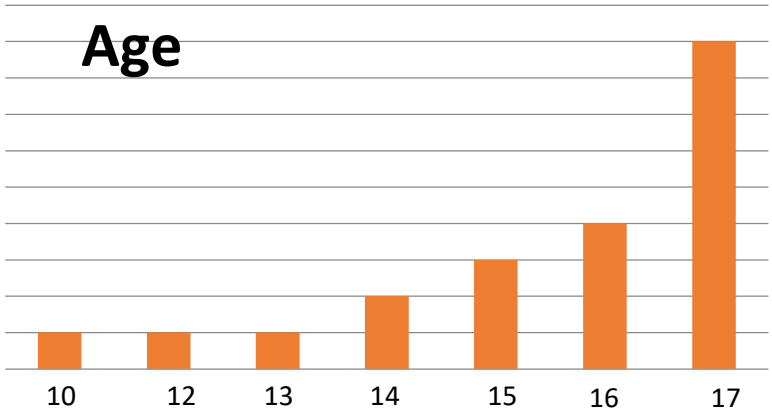
Children and adolescents Age, med (range) years	40 15 (10-17)
Bdq (Lnz, Cfz) containing regimens incl. shorter modified treatment regimen	**21** 2
Dlm (Lnz, Cfz) containing regimens since	**19**
Interim treatment outcomes	
Failed	**0**
LTFU	**0**
Died	**0**
Cured + Treatment completed Bdq Dlm	**33** 16 17
Treatment continuing	**7**

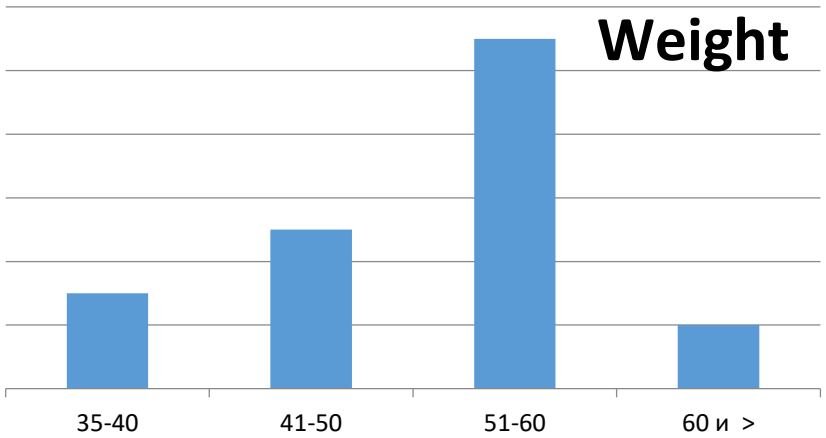
M/XDR-TB diagnosis

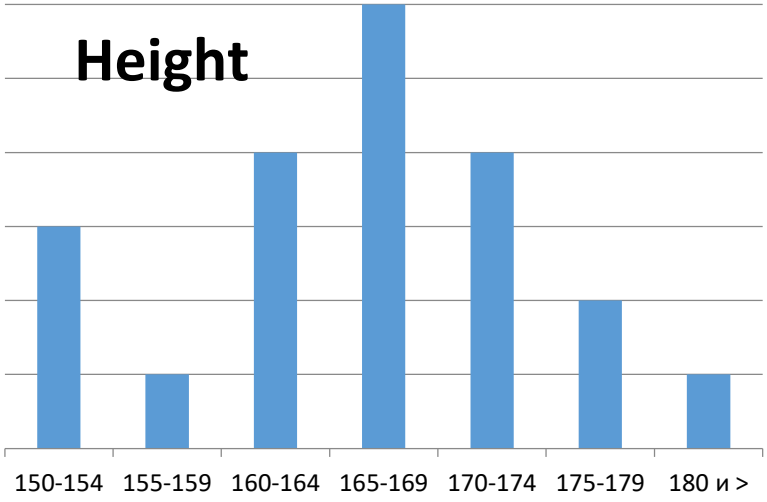
Degree of certainty of the diagnosis	
Full laboratory confirmation	**n=33**
XDR-TB	19
MDR-TB + FQ	6
MDR-TB + I	6
MDR-TB	2
Xpert/Rif + clinical + contact DR profile	**n=4**
XDR-TB	3
MDR-TB	1
Clinical + contact DR profile	**n=3**
XDR-TB	2
MDR-TB	1

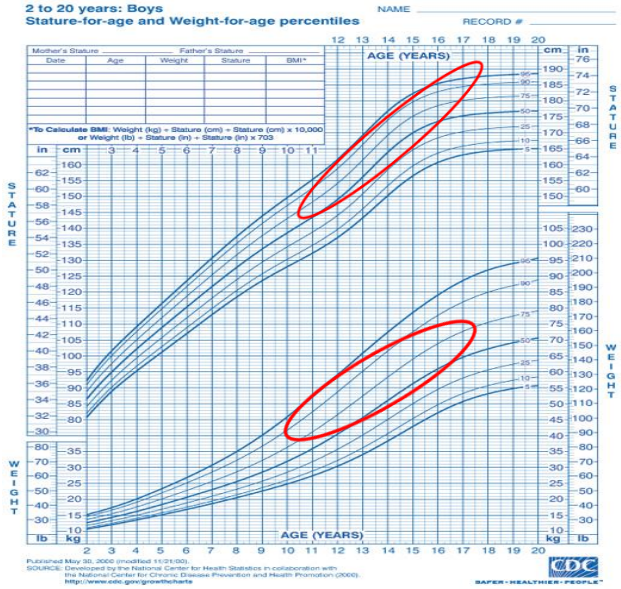
XDR-TB	**24**
MDR-TB+FQ	**6**
MDR-TB+I	**6**
MDR-TB	**4**

Patients characteristics. *n=33*









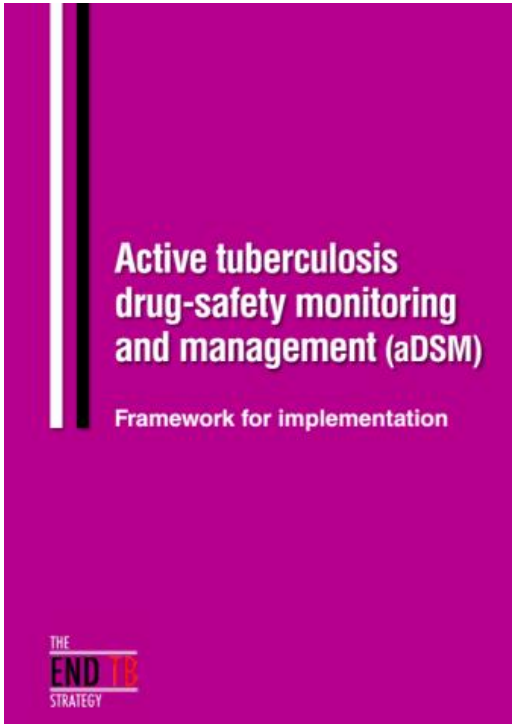
Comorbidity

	-
	-
	Myopia
	-
	Cerebral palsy
	Primary hypothyroidism, Myocardial dystrophy, Epilepsy
	Myopia
	Myopia, Nephroptosis
	-
	Cerebral palsy, Epilepsy
	Sensorineural hearing loss (before treatment)
	Anemia (iron deficiency)
	-
	-
	-
	-
	-
	-

Children and adolescents on new MDR-TB regimens adverse events

- Mg ↓ (4)
- Uric acid ↑ (4)
- QTcF prolongation (2)
- Eosiniphyles ↑ (2)
- Arthralgia (2)
- Urea ↑, Creatinine↑ (2)
- ALT↑, AST↑ (1)
- Glucose↑ (1)

SAE were not registered



Clinical Case

16 y.o. boy diagnosed with XDR-TB (family contact)

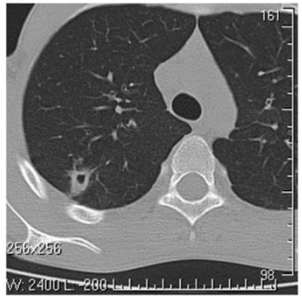
- **July, 2015**
  - Sputum Smear (SS) +
    Sputum Culture (SC) +
  - X-ray and CT: unilateal lesion, cavitation
  - DST: **R H E Km Pto Ofx, Lfx**
  - Treatment started:
    Z Cm Mfx Pto Pas Cs

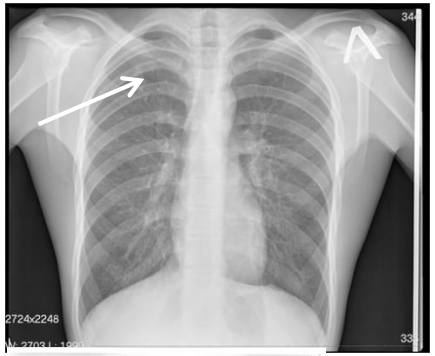
- **October, 2015**
  - X-ray, CT further deterioration
  - SS + SC + continuation (4 mo.)
  - Lost of appetites, weight lost
  - New treatment started:
    Bdq Cfz Lzd Tzd Imp Amx/clv
  - **CV port system was implanted**

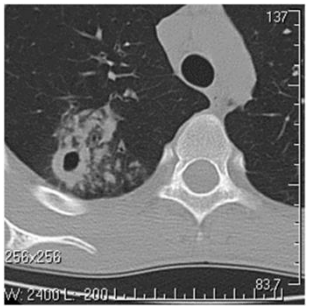
- **November, 2015**
  - On new treatment:
  - **SS - SC - conversion in one month !**

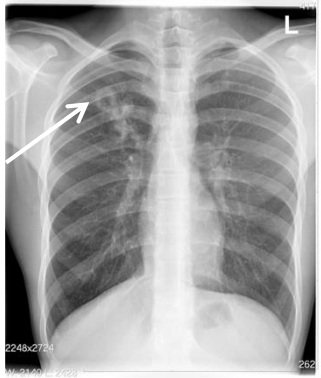
- **May, 2016**
  - SS -, SC -
  - Significant radiological improvement!
    Closure of cavitary lesion
  - On out-patient treatment. Clinically everything is ok

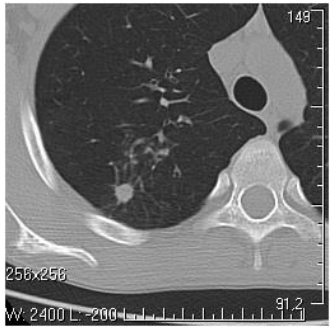
- **No significant AE**
- **October 2017 – CURE !!!**

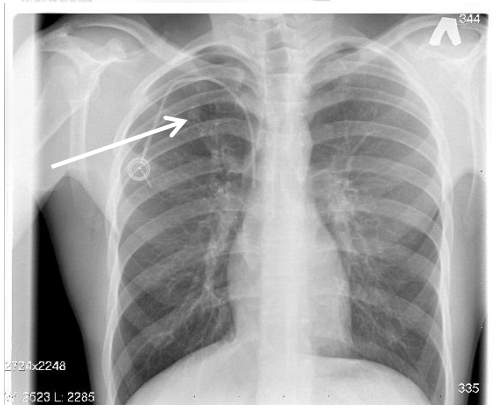












Conclusions

- Our patient series will help increase the global knowledge base for pediatric M/XDR-TB patients treated with new drug-containing regimens under programmatic conditions.

- Interim results on new drug-containing regimens use in children and adolescents show:
  - Good safety profile and
  - Excellent treatment outcomes.

- The experience gained can promote further expansion of this approach for children and adolescents with M/XDR-TB.

Thank you