

Shortages of Drugs and Biologicals Used for Tuberculosis

Securing Adequate Supplies for each Patient

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Introduction

Why are we discussing shortages in 2013?

- *U.S. TB patients and U.S. TB Programs have experienced recurring difficulty accessing first- and second-line TB drugs , and are now also experiencing a Tuberculin Skin Test reagent shortage*

Issues:

- *Shortages*
- *Climbing costs*
- *Multi-step processes for procurement*
- *Out-of-reach costs for uncovered patients*
- *Stress on programs*

BACKGROUND - I: TB CONTROL

Patient perspective and the new Stop TB Strategy:

The new WHO Stop TB Strategy combines the 5 pillars of the DOTS strategy with elements of the DOTS expansion strategy [WHO 2006]. The 5 pillars of DOTS are:

- political commitment;
- a quality-assured laboratory network for bacteriological diagnosis of TB;
- standardized treatment with short course regimen;
- uninterrupted drug supply; and
- accountability through a recording and reporting system, supervision, monitoring and evaluation.

Essential Components of a National TB Program

International Standards for TB Control programs, developed by the TB Coalition for Technical Assistance (TBCTA)

- *An uninterrupted supply of quality anti-TB drugs*

Essential Components of a TB Prevention and Control Program, CDC's Advisory Committee for the Elimination of Tuberculosis (**ACET**), MMWR, 1995

- *Ensure that patients who have TB receive appropriate treatment until they are cured*
- *Treat patients without consideration of their ability to pay*

WHO Stop TB Strategy: Components and Implementation

- ❑ **6 components**
- ❑ **Component 1: Pursuing high-quality DOTS expansion and enhancement**
- ❑ **Component 1, Element 4: An effective drug supply and management system**
 - *An uninterrupted and sustained supply of anti-TB drugs is fundamental to TB control*
 - *A reliable system of procurement and distribution of anti-TB drugs should be in place*
 - *Anti-TB drugs should be available free of charge, both because patients are poor and may not afford them, and because treatment has benefits that extend to society*
 - *Legislation related to drug regulation should be in place*

BACKGROUND - II: DRUG SHORTAGES

Reasons for TB drug shortages

- ❑ **Most common: problems with manufacturing**
 - *May include non-specific discoloration of product, glass shards, metal filings, fungal or other contaminants, --especially an issue with injectable drugs*
- ❑ **Delays in manufacturing or shipping**
- ❑ **Active pharmaceutical ingredient (API) shortages**
- ❑ **Increasing demand outpacing supply**

Others challenges contributing to TB drug shortages

- ❑ Passive surveillance/reporting**
- ❑ Short-dated medications**
- ❑ Single sources for some drugs**
- ❑ Lengthy procurement processes for certain drugs**
- ❑ Manifestations of market forces, e.g., hoarding, price increases and gouging, market abandonment**

Results of TB drug shortages on patient care

- ❑ Delays in treatment or procedures**
- ❑ Rationing or restriction of drugs**
- ❑ Need to use less effective alternative drugs**
- ❑ Occurrence of medication errors and adverse events related to using alternative drugs**
- ❑ Increases in drug costs**
- ❑ Increases in ancillary costs**
- ❑ Staff time dedicated to drug procurement and labor costs for these activities**

Effects of TB drug shortages on programs

- ❑ Impacts are felt by patients, programs, providers**
- ❑ TB programs lose credibility, and cannot meet core functions**
- ❑ TB disease manifestations may worsen**
- ❑ Patients may acquire further drug resistance**
- ❑ Further TB transmission may occur**
- ❑ Failed ability to respond to outbreaks: perfect storm – shortage of drugs, overwhelming disease burden**

SPECIFIC TB DRUG SHORTAGES

Current INH Drug Shortage

- ❑ In November 2012, CDC was notified of a national shortage of INH
- ❑ MMWR Notes from the Field was published December 21, 2012

Morbidity and Mortality Weekly Report

Notes from the Field

National Shortage of Isoniazid 300 mg Tablets

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INH suppliers

- ❑ **3 suppliers of INH in the US: Teva, Sandoz and VersaPharm**
- ❑ **All 3 reported shortages of 300mg tablets and many had shortages of 100mg tablets**
- ❑ **Reasons disclosed by suppliers:**
 - *Teva had a manufacturing issue that was a non-specific discoloration of a large amount of manufactured product*
 - *Sandoz had a lack of API*
 - *VersaPharm had several problems and decided to leave the market for at least a year*
- ❑ **No other recent shortages of INH had been reported globally**

**NATIONAL TB CONTROLLER'S
ASSOCIATION SURVEY OF TB DRUG
SHORTAGES**

Background for NTCA Surveys

- ❑ **NTCA has had many reports of TB programs having difficulty procuring TB medications**
- ❑ **In response, to assess if there were a national problem with acquiring anti-TB medications (2010), and to assess the extent of the INH problem (2013), NTCA conducted two nation-wide surveys**

Methods

- ❑ **Two different surveys sent to assess both second-line TB drug (SLD) and INH shortages**
- ❑ **Eligibility criteria**
 - *Eligible participant was the designated TB Controller of any level program: state, local, county*
 - *Participant had to have a registered and functioning email address*
 - *SLD survey sent in November 2010 and INH survey sent January 2013*
- ❑ **Surveys created on SurveyMonkey**
- ❑ **Surveys distributed by email and completed via the internet**
- ❑ **Answers stored and analysis conducted using SurveyMonkey software**

RESULTS

SLD Shortage Survey Results, 2010

54% response rate (33/61)

Characteristics of TB programs responding to NTCA survey, 2010

Characteristic	Total (n, %)
Type of TB Program	
Local	4 (12)
State	29 (88)
Number of TB cases reported per year	
0 – 50	7 (21)
51 – 100	10 (30)
> 100	16 (48)
Number of MDR cases reported per year	
0	7 (21)
1 – 10	20 (61)
> 10	5 (15)
Missing	1 (3)
Pay HRSA 340B Drug Pricing Program prices	25/29 (86)

SLD shortage experiences of TB Controllers in the US, NTCA SLD Survey 2010

Characteristic	Total (n/N, %)
Faced any challenges obtaining MDR-TB medications* in the past 5 years	21/26 (81)
<i>If yes, which ones?</i>	
<i>Nationwide shortage</i>	21/21 (100)
<i>Shipping delays</i>	15/21 (71)
<i>Medications too expensive for their program</i>	13/21 (62)
<i>Medications too expensive for insured patients</i>	8/20 (40)
<i>Medications too expensive for uninsured patients</i>	10/20 (50)
<i>Delays caused by the IND/IRB process</i>	10/21 (48)
<i>Payor bureaucracy</i>	7/19 (37)
Adverse effects due to challenges	
<i>Delay in starting treatment</i>	11/19 (58)
<i>Treatment lapse/interruption</i>	6/19 (32)
<i>Inadequate regimens</i>	6/19 (32)
<i>Substantial staff time tied up with drug procurement</i>	13/19 (68)

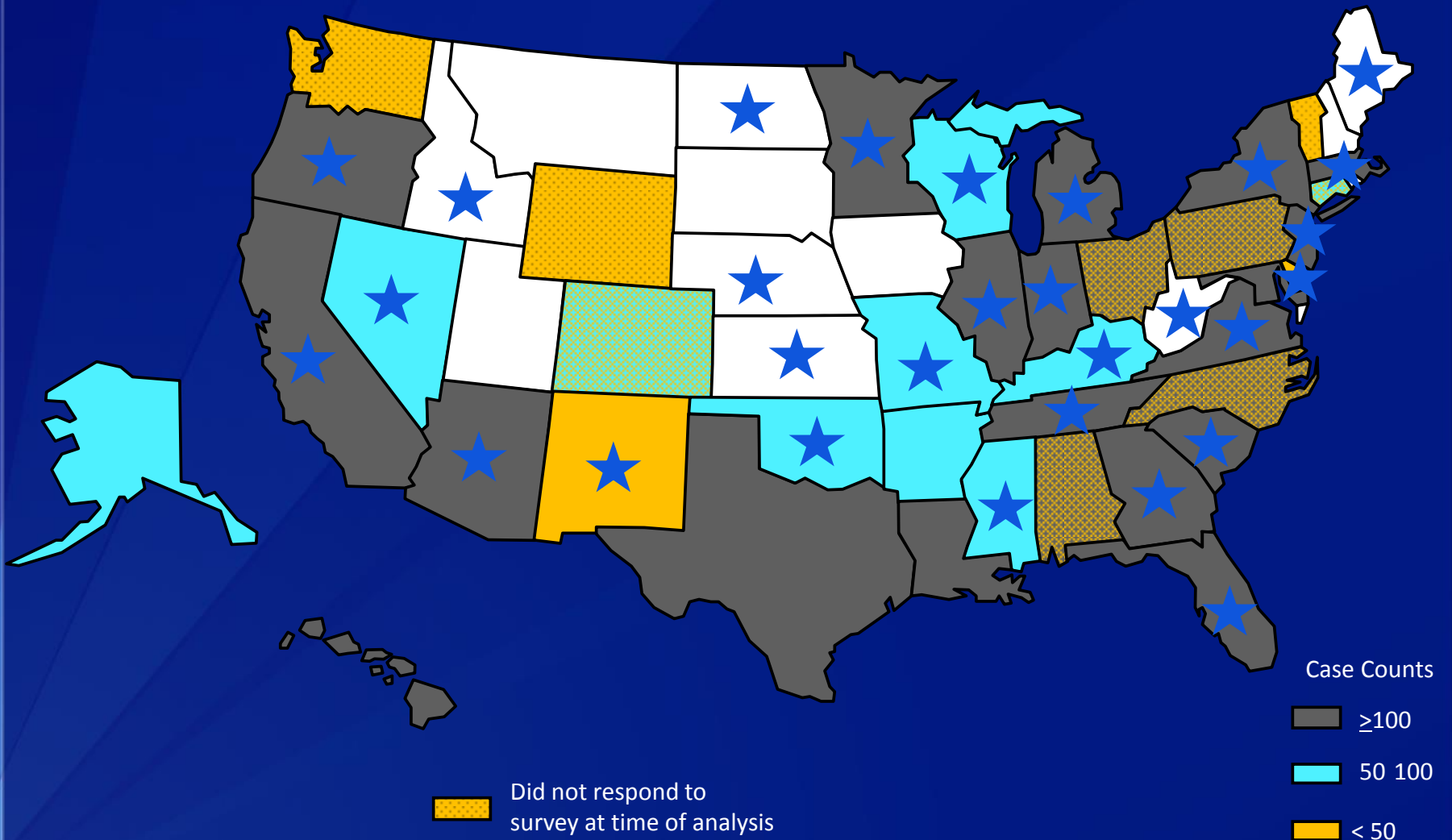
* MDR medications include Capreomycin, Amikacin, Kanamycin, Moxifloxacin, Levofloxacin, PAS, Cycloserine, Ethionamide, Linezolid, Clofazamine

INH Survey Results, NTCA, January 2013

- Of 68 surveyed jurisdictions, 42 (62%) responded

Characteristic	Total (n, %)
Type of TB Program	
<i>Local (San Francisco, San Diego, NYC)</i>	4 (10)
<i>State</i>	38 (90)

States reporting difficulty getting INH, by 2011 TB case counts, United States, 2012 - 2013



Number and percentage of TB programs experiencing challenges in obtaining INH, 2012 – 2013

Characteristic	No.+	%
Procurement		
<i>Difficulty obtaining INH in last month</i>	33/42	79
<i>Programs able to obtain 100mg INH tablets during 300mg shortage</i>	18/30	60
<i>Changed suppliers to procure medications</i>	20/29	69
Anticipated Supply		
<i>No longer had supply of INH at time survey</i>	6/39	15
<i>Would no longer have supply</i>		
<i>Within ≤ 1 month of survey</i>	12/29	41
<i>Within 1 - 3 months of survey</i>	13/29	45

Number and percentage of TB programs experiencing challenges in obtaining INH in the US, 2012 – 2013

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<i>>1 of above activities</i>	31/37	84
<i>Answering calls from patients, providers, nursing homes, or corrections</i>	32/39	82

CDC RESPONSE

ACET Advisory Group for MDR TB

- ❑ **Working group established in 2010 to address concerns about MDR TB drug shortages**
- ❑ **Problem statement**
 - *TB control programs in the US do not have an uninterrupted supply of drugs needed to treat drug resistant TB*
 - *Inadequate or interrupted treatment of drug resistant TB can lead to acquisition of further drug resistance and further spread of drug resistant TB and death, which substantially add to financial and public health costs*
 - *The current system for managing drug shortages is not sufficient to ensure an uninterrupted supply of TB drugs*
 - *The interrupted supply of drugs for drug resistant TB poses a threat to the control of drug resistant TB, to the mandate that public health assures the appropriate treatment of TB, and to the overall public health in the US*

Publication of results of the NTCA SLD survey MMWR, January 18, 2013 / 62(02);23-26

Morbidity and Mortality Weekly Report

Interruptions in Supplies of Second-Line Antituberculosis Drugs — United States, 2005–2012

Second-line drugs (SLDs) are essential for treating multidrug-resistant and extensively drug-resistant tuberculosis (MDR TB* and XDR TB†). Drug shortages, in which supplies of all clinically interchangeable versions of a given Food and Drug Administration (FDA)–regulated drug become inadequate to meet actual or projected user demand, have been well-documented in many areas of medicine; for several years, drug shortages in the United States have affected the availability of SLDs for treatment of TB. In November 2010, a nationwide survey of TB control programs conducted by the National Tuberculosis Controllers Association (NTCA) indicated that shortages and other problems that hinder access to SLDs interfere with patient care and could promote the development of drug resistance as well as the transmission of drug-resistant *Mycobacterium tuberculosis*. This report focuses on the growing issue of TB drug shortages and summarizes the findings of that survey, which indicated that 26 (79%) of the 33 responding health departments, representing approximately 75% of the U.S. TB burden, reported MDR TB during 2005–2010. Of these 26, 21 (81%) faced dif-

srupted TB disease, isoniazid, rifampin, pyrazinamide, and ethambutol are the four first-line drugs used worldwide as a 6-month standard regimen. In contrast, MDR TB generally requires 18–24 months of treatment with five or six drugs that are less effective, more toxic, and more costly than first-line drugs. As a result, MDR TB causes greater morbidity, and, overall, patient outcomes are worse.

Currently, CDC and FDA are collaborating to identify solutions to ameliorate a national shortage of isoniazid (*I*). SLD shortages also can disrupt treatment of drug-susceptible TB in patients who cannot tolerate first-line drugs and can complicate the treatment of MDR TB and XDR TB, putting patients and communities at greater risk for morbidity and mortality. For example, in April 2011, shortages of capreomycin and amikacin, two SLDs used to treat MDR TB and XDR TB, posed a serious threat for a father and his infant who had MDR TB. Despite intensive efforts by public health personnel to obtain the two drugs, the initiation of treatment was delayed by 8 days for both patients, prolonging the father's infectious period and thereby increasing the risk for transmission to the

CDC Response

- ❑ In mid-January 2013, CDC was notified that VersaPharm will not have INH until 2014
- ❑ A CDC health advisory notification (HAN) was released
- ❑ CDC worked with FDA and Teva to establish emergency allocations guidelines to ensure that the highest-risk patients can receive this medication.



This is an official
CDC HEALTH ADVISORY

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CDCHAN-00340

Recommendations for Drug Allocation, Tuberculosis
Prevention, and Patient Care During Isoniazid Shortages

Heath Advisory Note – Priorities for INH allocation

- ❑ Patients being treated for active TB disease
- ❑ Patients being treated for latent TB infection if they belong to any of the following categories:
 - *Were diagnosed during a contact tracing of a patient with contagious TB,*
 - *Are immunocompromised (e.g., persons with HIV infection, or receiving immunomodulating medications), or*
 - *Are less than 5 years of age.*

Tubersol

- ❑ **Sanofi-Pasteur is now reporting a supply interruption for Tubersol.**
- ❑ **CDC suggests using Applisol until supplies of Tubersol return to normal.**
- ❑ **DTBE will continue to provide updates to State and local health departments on this shortage as new information becomes available.**
- ❑ **DTBE Program Consultants will be checking in with TB programs regularly to assess needs.**

NEXT STEPS

What are challenges to an uninterrupted supply of anti-TB drugs that have been seen in the U.S.?

Medications	Challenges to an uninterrupted supply
<i>Kanamycin</i>	<i>No US manufacturer</i>
<i>Streptomycin</i>	<i>Single US manufacturer; increased demand resulted in Aug/Sept 2011 shortage</i>
<i>Amikacin</i>	<i>Materials short for production; overseas FDA inspection pending</i>
<i>Capreomycin</i>	<i>Single US manufacturer. Price increase x 10 since change in manufacturer (2007: \$11.7/1 gram vial; 2010: \$137/1 gram vial after manufacturer changed from Eli Lilly to Akorn); 2011: New report of ~\$300/1 gram vial</i>
<i>Cycloserine</i>	<i>Single US manufacturer; price doubled when license transferred from Eli Lilly</i>
<i>PAS</i>	<i>Single US manufacturer</i>
<i>Ethionamide</i>	<i>Not immediately available via wholesaler</i>
<i>Linezolid</i>	<i>Very expensive</i>
<i>Clofazamine</i>	<i>Requires IND and local IRB approval, process takes 8-10 wks</i>

TB Drugs that were in short supply as of December 2012

- ❑ **Amikacin: material in short supply for production; allocation only**
- ❑ **Capreomycin: single manufacturer; allocation only; cost**
- ❑ **Clofazimine: IND**
- ❑ **Cycloserine: single manufacturer; cost (price doubled when license transferred)**
- ❑ **Ethionamide: not immediately available via wholesaler**
- ❑ **INH (isoniazid) 300 mg: not currently available**
- ❑ **Linezolid: cost**
- ❑ **PAS (4 amino-salicylic acid): single manufacturer**
- ❑ **Rifapentine (for treatment of latent TB infection): cost**

What can DTBE do?

- ❑ Consult with TB programs when shortages are identified**
- ❑ Share information about drug availability with programs**
- ❑ Provide evidence of impact of drug shortages and increasing drug costs**
- ❑ Collaborate with FDA to reduce impact of drug shortages**
- ❑ Stockpile drugs**
- ❑ Hold Investigational New Drug (IND) protocols for specific drugs (Clofazimine, Kanamycin) to reduce the administrative burden on TB programs**

Where we are right now with the INH shortage

- ❑ As of March, FDA's website indicated that INH is available from both Teva and Sandoz**
- ❑ VersaPharm has notified customers that it will not be filling orders for INH until 2014**
- ❑ NTCA has assessed pricing information from the pharmacies where TB programs purchase INH. Prices for INH manufactured by Sandoz have been up to 35 times higher after the shortage than before it.**
- ❑ After DTBE and FDA spoke with Sandoz, the company said it would consider offering INH at concessionary pricing to health departments**

Potential Long-Term Solutions

- ❑ **Establish regulatory requirements for early notification to FDA of potential shortages and of plans for product discontinuations**
- ❑ **Create a national or regional MDR TB drug repository**
- ❑ **Offer financial incentives (e.g., tax credits) to drug makers to produce specific drugs in shortage**
- ❑ **Work with the HHS Supply Center at Perry Point to serve as a stockpile or act as an agent under a vendor managed inventory program with manufacturers**
- ❑ **Work with FDA to develop ways to facilitate obtaining drugs from The Global Drug Facility (GDF) or directly from overseas manufacturers**

Progress has been made - I

- ❑ **President's Executive Order**
- ❑ **FDA documents**
 - *A Review of FDA's Approach to Medical Product Shortages*
 - *Economic Analysis of the Causes of Drug Shortages*
- ❑ **FDA already works with manufacturers, and reports having prevented 38 drug shortages in 2010, 195 in 2011, and 150 as of November, 2012**

Progress has been made - II

- ❑ DTBE has submitted for IRB approval an Investigational New Drug (IND) protocol for clofazimine, which has a history of safe and effective use for leprosy and MDR TB.**
- ❑ The protocol would provide access to clofazimine for patients who have limited other options, i.e., persons with MDR TB, persons with XDR TB, and persons who have had adverse events with other medications.**
- ❑ CDC will be responsible for the IRB-approved IND protocol that programs can rely on, but TB programs will still need to submit a single IND form for each patient to FDA.**

2011 President's Executive Order

- ❑ **President Obama issued Executive Order directing FDA and DOJ:**
 - *To help reduce and prevent disruptions in the supply of lifesaving drugs.*
 - *To use appropriate administrative tools, including authority to interpret and administer reporting requirements, to require manufacturers to provide adequate advance notice of discontinuances that could lead to shortages of drugs*
 - *To expand efforts to expedite regulatory reviews, including reviews of new drug suppliers, manufacturing sites, and manufacturing changes*
 - *To have FDA report to DOJ any findings that shortages have led market participants to stockpile drugs or sell them at exorbitant prices*

Reflections

- ❑ **Participation of CDC, FDA, and other federal agencies in addressing this issue in paramount**
- ❑ **DTBE/CDC in its capacity of overseeing the National TB Program's prevention and control activities needs to consider undertaking a new role that includes:**
 - *Dashboard*
 - *Warehousing*
 - *Facilitating access to alternative drug sources*

FDA Drug Shortage Websites

- ❑ <http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050792>
- ❑ drugshortages@fda.hhs.gov

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