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This passage discusses the challenges of eradicating tuberculosis (TB), particularly when it comes to strains of the bacteria that are resistant to multiple drugs, known as **Multi-Drug-Resistant (MDR-TB)** and **Extensively Drug-Resistant (XDR-TB)** strains.

### **Key Points:**

### **1. Transmission of MDR/XDR-TB**

* To eradicate TB, it's crucial to reduce the spread of **MDR and XDR-TB** strains. These are strains of **Mycobacterium tuberculosis** that have developed resistance to the standard drugs used to treat TB.

### **2. Initial Assumptions About Fitness**

* **Fitness** refers to the bacteria's ability to grow, survive, and spread.
* Initially, it was believed that drug-resistant strains would have **reduced fitness** because the mutations that make them resistant would also make them weaker—meaning they would grow more slowly and be less likely to spread.

### **3. Reality of MDR/XDR-TB Fitness**

* While many resistant strains do have compromised fitness (they are weak and are only found in one or a few patients), some strains of MDR/XDR-TB are highly transmissible and can cause large outbreaks. This means that not all resistant strains are weak—some are quite strong and can spread effectively.

### **4. Fitness Costs of Resistance Mutations**

* Most antibiotics work by targeting essential bacterial functions, like how the bacteria grow and reproduce.
* When TB bacteria develop mutations that make them resistant to these antibiotics, these mutations often come with **fitness costs**. This means the bacteria might grow more slowly or be less viable (less able to survive) because the mutations disrupt important functions.

### **5. Variation in Fitness Costs**

* The **fitness costs** of resistance mutations can vary depending on the specific mutation. Some mutations might make the bacteria much weaker, while others have only a small effect on the bacteria's fitness.

### **6. Compensatory Mutations**

* Sometimes, the bacteria can develop **secondary mutations** that compensate for the fitness costs of the initial resistance mutation. These compensatory mutations help restore the bacteria's fitness, allowing them to grow and spread more effectively, despite being resistant to drugs.

### **Summary:**

To eradicate TB, reducing the spread of drug-resistant strains is crucial. While some resistant strains are weak and spread poorly, others are highly transmissible and can cause outbreaks. Drug resistance often comes with a fitness cost, making the bacteria grow more slowly or survive less well. However, the severity of this fitness cost varies, and some bacteria can develop compensatory mutations that help them regain their strength, allowing them to continue spreading even after becoming resistant to drugs.

This passage discusses how **compensatory mutations (CM)** work in **Mycobacterium tuberculosis** to help the bacteria overcome the negative effects (fitness costs) that come with developing drug resistance. Here's a breakdown of the key points:

### **1. Compensatory Mutations (CM)**

* **Compensatory Mutations (CM)** are specific to each antibiotic. They help the bacteria cope with the harmful effects that arise when they develop resistance to a drug.
* These mutations work by counteracting the negative impact that the resistance mutations have on the bacteria’s ability to grow and survive.

### **2. CM and Fitness Costs**

* **Fitness Cost**: When a bacterium develops a mutation that makes it resistant to an antibiotic, this mutation often comes with a fitness cost, meaning the bacterium might grow slower or be less viable.
* **CM and High Fitness Costs**: Generally, compensatory mutations are more common in bacteria that have developed resistance mutations with **high fitness costs**. The more the resistance mutation weakens the bacterium, the more likely it is to acquire compensatory mutations to regain its fitness.
* **Rifampicin (RIF) Example**: However, in the case of **rifampicin resistance**, compensatory mutations are most frequently found in strains with the **Ser450Leu** mutation, which actually carries the **least fitness cost**. This might seem counterintuitive, but it suggests that even minor fitness costs can drive the evolution of compensatory mutations.

### **3. Fitness Costs and Transmission**

* **High vs. Low Fitness Costs**: The relative fitness costs of resistance mutations and the presence of compensatory mutations explain why some mutations are commonly found in highly transmissible strains, while others are rare or never found in clinical samples.
* **Highly Transmitted Clusters**: Mutations that have lower fitness costs or that are well compensated by CMs are more likely to be found in strains that spread widely among people.

### **4. Evolution of Drug Resistance**

* **CM and Bacterial Evolution**: Compensatory mutations provide insight into how drug resistance affects bacteria and how bacteria can evolve to overcome the stress caused by antibiotics.
* **Paradigm for Evolution**: The way bacteria develop resistance and then evolve compensatory mechanisms to survive and spread illustrates a broader pattern of how mycobacteria (the bacteria that cause TB) can adapt in response to environmental stresses, such as the presence of antibiotics.

### **Summary:**

Compensatory mutations help **M. tuberculosis** cope with the negative effects of drug resistance. These mutations vary depending on the antibiotic and are more common when the resistance mutation imposes a high fitness cost. However, even mutations with low fitness costs, like the Ser450Leu mutation for rifampicin resistance, can frequently have compensatory mutations. The presence and effectiveness of these compensatory mutations help explain why some drug-resistant strains spread widely while others do not. Overall, compensatory mutations illustrate how bacteria can evolve to survive in the face of antibiotic stress, helping them maintain their ability to grow and spread even after developing resistance.

According to the World Health Organization (WHO) [1,2], approximately 10 million people develop tuberculosis (TB) each year. Among them, around half a million are infected with Mycobacterium tuberculosis (M. tb) strains that are resistant to rifampicin (RIF-R), with 78% of these cases also resistant to isoniazid (INH), a condition known as Multi-Drug-Resistant TB (MDR-TB). Of the MDR-TB cases, about 5-8% also exhibit resistance to a fluoroquinolone (FQ) and one of the injectable drugs, such as capreomycin, kanamycin, or amikacin, classifying them as Extensively Drug-Resistant TB (XDR-TB). MDR-TB strains that are resistant to FQs alone are termed pre-XDR-TB. Recently, the WHO updated the definition of XDR-TB to indicate resistance to the FQs levofloxacin or moxifloxacin and at least one of the group I agents—bedaquiline or linezolid [3]. However, since the studies reviewed here were conducted before this change, the previous definition of XDR-TB will be used. MDR and XDR-TB strains require longer and more costly treatments than drug-sensitive (DS) strains, with only about 57% [2,4] of MDR-TB patients achieving cure following treatment. However, recently introduced treatment regimens have shown cure rates of up to 80% [5–8]. Given these challenges, drug-resistant TB strains pose a significant obstacle to TB control and eradication efforts.

Shortly after isoniazid (INH) was introduced as a treatment for tuberculosis (TB) in the 1950s, Middlebrook discovered that most INH-resistant Mycobacterium tuberculosis (M. tb) strains were less virulent in guinea pigs [9–12]. This observation led to the belief that drug-resistant (DR) strains were inherently weaker, or less fit, than drug-sensitive (DS) strains. Since antibiotics typically target enzymes essential for bacterial survival, it is logical that resistance-conferring mutations, which alter these critical enzymes, could result in a loss of fitness. This would mean that resistant bacteria might grow more slowly, be transmitted less frequently, and potentially cause less severe disease [13–17]. However, resistant strains can also develop secondary compensatory mutations (CM) that partially or fully restore the fitness lost due to the resistance-conferring mutations. These compensatory mutations vary depending on the antibiotic, as they counteract the specific functions compromised by the resistance mutations [18]. Although compensatory mutations are generally more common in strains where resistance mutations impose significant fitness costs, the opposite is true for RIF-R mutations, as discussed below.