NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Antibiotic Resistance in a Russian Prison: Playing with the Spread of Tuberculosis

by
Christian Angeles, Isabella Villano, and Andrea Nicholas
Department of Neurobiology and Behavior
University of California, Irvine

Background Handout

To prepare for the game you will play and discuss in class, please read the background information below and view the PBS video clip "Evolution Primer #6: Why Does Evolution Matter Now?" (available at <https://youtu.be/6jBD8xfbf4Y>. Alternatively, the World Health Organization provides similar informaiton in an article entitled "Tough measures in Russian prisons slow spread of TB" at <http://www.who.int/bulletin/volumes/84/4/news30406/en/>.)

Tuberculosis (TB) is a potentially fatal bacterial infection caused by the aerobic bacillus *Mycobacterium tuberculosis*. The disease is typically transmitted via contaminated, airborne droplets that result from coughing or sneezing (9). Though often associated with respiratory infections, *M. tuberculosis* may infect numerous regions of the body, including the nervous system, kidneys, and even skin (8). Found throughout the world, TB accounted for nearly 9 million new cases and 1.5 million deaths in the year 2013. The disease is especially prevalent in developing and low-income regions, where proper prevention and treatments are difficult to implement. The risk of acquiring and dying from TB increases for those with compromised immune systems, such as individuals with HIV (9).

Today, reducing the spread and prevalence of TB is of major global concern and has been incorporated into the World Health Organization (WHO) Millennium Development Goals (10). By 2011, about $5 billion dollars was spent on efforts to control TB (2). As a result, the rates of TB have begun a slow decline in many countries (9,10). Nevertheless, the ability of *M. tuberculosis* to develop antibiotic resistance is threatening such efforts (10). In recent years, cases of multiple drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) have begun to rise due to poor or improper use of antibiotic treatments and insufficient health facilities. Indeed, the first cases of XDR-TB were observed as recently as 2006, with 84 countries reporting cases of the illness by 2011 (6, 12). Similarly, in 2013, 480,000 people contracted or developed MDR-TB (9). MDR-TB is defined as *M. tuberculosis* infections that cannot be treated using the powerful antibiotics isoniazide and rifampicine, while XDR-TB strains are additionally resistant to the drug fluoroquinolone and an injectable TB treatment options like kanamycin and streptomycin (5, 6). Totally Drug Resistant tuberculosis (TDR-TB) has also been reported, though the WHO does not formally recognize the term and further research is necessary to define the illness (6, 11).

Strains of antibiotic TB are notably present in Russia and the former Soviet Union, and constitute a significant health risk for these nations (1–4, 7). Indeed, the city of Minsk, Belarus, was reported to have the highest levels of MDR-TB in the world. This is in part due to shortages of medications and increased poverty levels in formerly Soviet regions following the fall of the Soviet Union in the 1990s (4). One *M. tuberculosis* variant, Beijing B0/W148, is hypothesized to have originated in regions of Russia and spread throughout the country's population. This variant is now seen in many other regions of the world (1). The Beijing strains of TB, which are primarily found in China, and closely related W strains, first identified in the Eastern United States, are common disease causing strains of the tuberculosis bacterium (13). Research has shown that Beijing variants of *M. tuberculosis* are extremely adept at building antibiotic resistance, and have been shown to have the highest rates of multiple and extensive drug resistance when compared to other strains (1, 7, 13).

Prisons in Russia and the former Soviet Union are of specific importance, as their crowded conditions and a reduced quality of medical care are believed to aid the spread of TB and propagate new outbreaks of the illness, even in surrounding civilian populations. Proper identification and treatment of infected inmates could help slow the spread of the disease throughout these communities, as well as reduce the risk of TB transmission in the prisons. Thus, measures have been taken by the WHO to implement systems of diagnosing TB positive inmates, such as medical screenings and self-referral inmate questionnaires (2). However, new, quick and effective tests for diagnosing TB present higher costs and may be more difficult to acquire than slower, traditional methods. Improved medical technologies are currently being studied to discern the best techniques by which to identify people infected with *M. tuberculosis*, both inside and outside prisons, and may potentially lead to a reduction in outbreaks of the illness, as well as inhibit the development of further resistant strains (2, 4).

References

1. Mokrousov, I. 2013. Insights into the origin, emergence, and current spread of a successful Russian clone of *Mycobacterium tuberculosis. Clinical Microbiology Reviews* 26(2): 342–360. Doi: 10.1128/CMR.00087-12.
2. Winetsky, D., D. Negoescu, E. DeMarchis, O. Almukhamedova, A. Dooronbekova, D. Pulatov, …, and J. Goldhaberfiebert. 2012. Screening and rapid molecular diagnosis of tuberculosis in prisons in Russia and Eastern Europe: a cost-effectiveness analysis. *PLOS Medicine* 9(11): e1001348. Doi: 10.1371/journal.pmed.1001348.
3. Mokrousov I., A. Vyazovaya, T. Otten, V. Zhuravlev, E. Pavlova, L. Tarashkevich, …, and O. Narvskaya. 2012. *Mycobacterium tuberculosis* population in Northwestern Russia: an update from Russian-EU/Latvian border region. *PLoS ONE* 7(7): e41318. Doi: 10.1371/journal.pone.0041318.
4. Skrahina, A., H. Hurevich, A. Zalutskaya, E. Sahalchyk, A. Astrauko, W. Gemert, …, and M. Zignol. 2012. Alarming levels of drug-resistant tuberculosis in Belarus: results of a survey in Minsk. *European Respiratory Journal* 39(6): 1425–1431. Doi: 10.1183/09031936.00145411.
5. Veluchamy, M., Madhavan, R., Rajesh, S.N. 2013. katG gene as a surrogate molecular marker leading to cause drug resistance in *Mycobacterium tuberculosis* isolates. *American Journal of Infectious Diseases and Microbiology* 1(5): 86–91. Doi: 10.12691/ajidm-1-5-2.
6. World Health Organization. 2016. Tuberculosis fact sheet [web page]. Retrieved 30 June, 2016, from <http://www.who.int/mediacentre/factsheets/fs104/en/>.
7. Vyazovaya, A., I. Mokrousov, N. Solovieva, A. Mushkin, O. Manicheva, B. Vishnevsky, V. Zhuravlev, and O. Narvskaya. 2015. Tuberculous spondylitis in Russia and prominent role of multidrug-resistant clone *Mycobacterium tuberculosis* Beijing B0/W148. *Antimicrob Agents and Chemotherapy* 59(4): 2349–57. Doi: 10.1128/AAC.04221-14. Epub 2015 Feb 2., <http://www.ncbi.nlm.nih.gov/pubmed/25645851>.
8. Ngan, V. 2003. Cutaneous tuberculosis [web page]. *DermNet NZ.* Retrieved 30 June, 2016, from <http://www.dermnetnz.org/bacterial/tuberculosis.html>.
9. World Health Organization. 2016. Tuberculosis: fact sheet [web page]. Retrieved 30 June, 2016, from <http://www.who.int/mediacentre/factsheets/fs104/en/>.
10. World Health Organization. 2015. Millennium Development Goals (MDGs) [web page]. Retrieved 30 June, 2016, from <http://www.who.int/mediacentre/factsheets/fs290/en/>.
11. World Health Organization. 2012. "Totally Drug-Resistant" tuberculosis: a WHO consultation on the diagnostic definition and treatment options [web page]. Retrieved 30 June, 2016, from <http://www.who.int/tb/areas-of-work/drug-resistant-tb/xdrconsultation/en/>.
12. Sagonda, T., L. Mupfumi, R. Manzou, B. Makamure, M. Tshabalala, L. Gwanzura, and R. Mutetwa. 2014. Prevalence of extensively drug resistant tuberculosis among archived multidrug resistant tuberculosis isolates in Zimbabwe. *Tuberculosis Research and Treatment* 2014: 1–8. Doi:10.1155/2014/349141.
13. Glynn, J.R., J. Whiteley, P.J. Bifani, K. Kremer, and D.V. Soolingen. 2002. Worldwide occurrence of Beijing/W strains of *Mycobacterium tuberculosis*: a systematic review. *Emerg. Infect. Dis. Emerging Infectious Diseases* 8(8): 843–849. Doi:10.3201/eid0805.020002.

Game Instructions

Materials

In order to complete the game activity, each prison team students should receive:

- Pair of dice
- A deck of playing cards
- 20 index cards, paper slips, or post-it notes (to represent prison inmates)
- Colored pens, pencil, or stickers (to mark antibiotic resistance)
- An open, flat space to layout cards

Set Up

- Students should organize into teams of 4-5. Each team will supervise one prison.
- Each team will receive a set of the above materials.
- Arrange 20 cards into 5 rows (4 index cards across). Each index card represents an individual inmate and their proximity to other inmates living in tight quarters.
- The deck of playing cards should be given to one teammate who will serve as the prison doctor and determine which antibiotic gets prescribed.
- The dice should be given to a different teammate who will determine infection.
- The other teammates will record the spread of antibiotic resistance using stickers or colored pens/pencils.

Play

1. *Roll one die to see how many of your inmates develop TB.* You may choose which inmates are sick. Mark their infectious status on their index cards. If you role a 3, then 3 inmates should be marked as infectious.
2. Each of your infected inmates is prescribed different antibiotics by the prison doctor. *Pull a playing card from the deck for each sick inmate and place it over their respective index card.* This will determine which of the following antibiotics they have been given: Hearts (isoniazid), spades (rifampin), diamonds (fluoroquinolones) and clubs (injectable second-line drugs such as amikacin, kanamycin, or capreomycin).
3. *If the card is 7 or lower then assume the inmate completes the course of antibiotics. If the card is 8 or higher (J,Q,K high, Aces low), then the inmate does not complete the course of antibiotics.* If they properly complete their treatment, the inmate (for this round) is considered cured. If all inmates are cured, repeat Step 1 until you have inmates who have not completed treatment. Once you have inmates who have not completed treatment move to Step 4.
4. If an inmates does not complete their treatment we assume they develop resistance to that treatment (antibiotic). *For inmates who develop resistance, make note of the antibiotic resistance on that inmate's index card,* for they are now infected with a bacterial strain that is resistant to that antibiotic and can pass that on to other inmates.
5. Next, *roll one die for each inmate who did not complete their antibiotic treatment (regardless of resistance) to determine if they exhibit outward symptoms.* 1–3=No, 4–6=Yes. Why are outward symptoms of TB important? If the inmates do not exhibit outward symptoms, they will be considered not infectious. If all inmates are not infectious then return to Step 1 and repeat. If they harbor any TB with antibiotic resistance they will retain that resistance.
6. If any inmates exhibit outward symptoms, *roll one die for each of them to determine how many people around them they will infect.* Choose nearby inmates and mark those that have been exposed. *Note:* An inmate can be infected by more than one infectious carrier at this time if they are in close proximity to both. If a carrier with resistance infects a new inmate, then the newly infected inmate will carry the resistant strain of the bacteria. Make note of that resistance on their index card immediately.
7. The newly infected inmates are administered antibiotics by the prison doctor. *Pull a playing card from the deck for each newly infected inmate and place it over the index card to determine which antibiotic they have been given:* Hearts (isoniazid), Spades (rifampin), diamonds (fluoroquinolones) and clubs (injectable second-line drugs such as amikacin, kanamycin, or capreomycin).
8. Inmates who are prescribed an antibiotic for which they already have resistance will not be cured. If the card is 7 or lower, and there is not resistance to the antibiotic treatment, then assume the inmate has completed the

course of antibiotics and is considered cured. If the suit is 8 or higher (J,Q,K high, Aces low), then the infected inmate did not complete their course of antibiotics and will not be cured.

9. At this point inmates may become resistant to more than one antibiotic. We will assume that the bacteria exchange resistance genes inside the carrier and begin to create a "superbug" that is resistant to both treatments. Next, *roll one die for each infected inmate to determine if they exhibit outward symptoms.* 1–3=No, 4–6=Yes. If the inmates exhibit outward symptoms, they will be considered infectious.
10. If an inmate is infectious, *roll one die to determine how many fellow inmates around them will become infected.* Randomly choose nearby inmates and mark the exposed as newly infected inmates. You may re-infect inmates who have already been exposed and treated. *If a carrier that has a resistant or multi-resistant form of TB infects the new inmates, make note of that transferred resistance on their Index card immediately.*
11. Repeat the process (Steps 7–10) two more times for a total of four full infection cycles. You should now observe a striking increase in inmates who are carrying multi-resistant TB
12. One student in each team should *take a picture of the prison inmates* with their cell phone to document the current inmate population.
13. *Exposure! Roll one die to determine how many of your inmates will be released from prison.*
14. *Pull a card off the deck for each released inmate.* If the suit is black, they begin a new life in the surrounding community. If the suit is red, they will quickly commit another crime and return to jail.
15. Trade all of your red card inmates to another classmate's prison and accept new inmates into your prison.
16. Consider your new inmates. Have carriers for different types of resistance entered your prison?
17. Play two more rounds of the TB infection game (Steps 7–10).

Questions

1. As you progressed through the game, did it become more difficult to effectively treat patients with antibiotics? What was the major reason this occurred?
2. As was discussed in the pre-reading activity, there are differing levels of antibiotic resistance among TB patients. For example, some TB strains are resistant to only some of the main forms of antibiotic, while others are resistant to almost all potential treatments. Looking back at your prison system, did any of your inmates develop TB resistance to all forms of antibiotic? What circumstances most resulted in this high level of resistance?
3. Consider the nature of a prison environment. Why might this particular institution be more at risk of experiencing a TB outbreak? Following that same logic, what other institutions might also carry some of the risk factors associated with prisons?
4. As you saw in the exposure portion of the game, humans, such as the swapped inmates, can carry infectious agents from one location to another. How did the number of sick inmates, strains of antibiotic resistant TB, and overall ability of your prison to treat your inmates change after the prisoner exchange? Speak to other prisons, particularly those who accepted any of your original inmates, to see if they experienced similar changes.
5. During the exposure portion of this activity, you were asked to release some inmates back into the general population. Even if the released inmate was successfully treated for TB in your prison and did not commit a new crime, how might they pose a threat to the general population? Moreover, was there any instance in which the released prisoner had not been successfully treated, or had developed a resistant form of TB? What might be true of the population outside of the prison that would make them highly susceptible to acquiring TB from your inmate?
6. In order to prevent potentially infectious inmates from transmitting TB to the general population, some prisons have established systems to help identify sick inmates. These may include surveys or, with the development of new technology, quick medical screens to diagnose TB. If you were really in charge of a prison, what methods might you employ in order to prevent released inmates from transmitting TB? Take time to consider the cost, speed, and effectiveness of the screening technique, as well as the cooperation of the inmate population.