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WHAT ARE THE ODDS OF "TUBERCULOSIS IS A HERITABLE DISORDER"?

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ABSTRACT

Introduction: Tuberculosis is an infectious disease caused by mycobacterium tuberculosis. One-third of the world's population is colonized by M. tuberculosis. For the great majority of people, M. tuberculosis is part of normal human physiology and flora and 90% of the people infected by M. Tuberculosis do not develop active tuberculosis. New discoveries suggest gestational sac is not sterile without any evidence of contaminants suggesting that human cells may produce bacteria. Evidence suggests host biology may dictate the transformation of M. tuberculosis to a pathogen causing tuberculosis. Of significance, not all immune compromised patients colonized with M. tuberculosis progress to tuberculosis and not all patients with diabetes colonized by M. tuberculosis develop tuberculosis suggesting that host biology and factors independent of host immunocompetence may determine the transformation of M. tuberculosis to a pathogen causing tuberculosis. **Objective:** To project odds of certainty that tuberculosis Is heritable based upon diverse observations that are either consistent or inconsistent with tuberculosis being heritable. **Methods:** We applied probability theory $R=1/X^2$ with R representing random occurrence and x representing a number of diverse observations that are either consistent or inconsistent with tuberculosis being heritable. **Results:** Consistent with the probability theory, the odds of Tuberculosis being a heritable disorder is %99.999. Furthermore, converging epidemiological clinical and genetic studies also suggest tuberculosis is a heritable disorder. **Discussion:** Tuberculosis is a heritable condition disorder that can be transmitted to new hosts. Yet, the human cells that produce M tuberculosis is unknown. Stem cells are the most likely origin.

INTRODUCTION

Tuberculosis Is an infectious disease caused by Mycobacterium Tuberculosis Bacteria. Tuberculosis primarily affects the lungs but it can also involve other parts of the body. It is estimated that one-third of the world's population is colonized by M. tuberculosis among those 90% of people colonized by mycobacterium tuberculosis do not develop Tuberculosis.[1,2] In 2022 an estimated 10.6 million people developed active tuberculosis resulting in 1.3 million deaths making it the second leading cause of death from an infectious disease after Covid 19.[1,2]

Tuberculosis has existed since antiquity

Of significance, not all immune compromised patients colonized with M. tuberculosis progress to tuberculosis and not all patients with diabetes colonized by M. tuberculosis develop tuberculosis suggesting that host biology and factors independent of host immunocompetence may determine the transformation of M. tuberculosis to a pathogen causing tuberculosis.

OBJECTIVE

To project odds of certainty that tuberculosis Is heritable based upon diverse observations that are either consistent or inconsistent with tuberculosis being heritable.

METHODS

We applied probability theory $R=1/X^2$ with R representing random occurrence and x representing a number of diverse observations that are either consistent or inconsistent with tuberculosis being heritable. Of significance, consistent with the framework of flipping a coin, potential flaws of statistical analysis - randomness and bias- have no effect on the accuracy of final outcome. As long as it is fair play without tricks it does not matter who flips the coin.

Observations represent a syntheses of cumulative data on tuberculosis from the following databases: the Cochrane Infectious Diseases Specialized Register; CENTRAL; MEDLINE; and Google scholar up to July 2023.

OBSERVATIONS

Microorganisms in fetus are not contaminants from the environment

In the last decade diverse molecular observations have revealed the existence of endogenous microorganisms in breast tissue[3], breast milk[4,5] endometrium[6], uterus[7]

amniotic fluid,[8,9] placenta.[10,11] Of significance, there is no evidence that they are contaminants from the environment suggesting that human cells may produce microorganisms.

Mycobacterium paratuberculosis

Fetal tissues from 5 of 58 cows were culture-positive for Mycobacterium paratuberculosis but were not manifesting signs of paratuberculosis.[12] This observation prompts several questions.

They were either contaminants from the cows or emerged from the fetal cells.

If they were contaminants from cows, a higher number of fetuses should have been positive.

53 fetuses were not colonized by mycobacterium paratuberculosis.

This observation is consistent with Mycobacteria paratuberculosis was internally produced and inconsistent with contamination.

Some infections develop independent of contamination

Since the introduction of the germ theory dating back to the mid 19th century most human infections including tuberculosis have been viewed as foreign invasions by foreign microorganisms acquired by contamination.[13]

It has been demonstrated that some human infections may develop independent of contamination.[14-19] There is compelling evidence to suggest Tinea versicolor[17,18], Pylori[14,15] and myiasis[15,16] may be endogenous infections. Clinical, epidemiological and molecular evidence suggests Tinea versicolor, H.pylori may not be contaminants from the environment and yet under certain conditions - which are almost always associated with the alteration of host biology-they may become disease inducing pathogens.

Human cells or tissues may produce microorganisms and infections.

Mycobacterium tuberculosis part of normal human physiology

Mycobacterium tuberculosis belongs to normal flora with two third of the world's population hosting it and 90 percent of infected people without developing active tuberculosis.[19,20,21] suggesting that mycobacterium tuberculosis is part of normal human physiology. This is a point of emphasis: 90 % of infected people do not develop active tuberculosis .We can infer that for a large population M. tuberculosis part of normal human physiology.

Also, humans are the predominant reservoir of M. tuberculosis[19,20] and Mycobacteria typically are free-living environmental saprophytes which do not proliferate in the inanimate environment[18] suggesting that T. Mycobacteria may be endogenous.

TB is heritable

Twin studies show an increased concordance rate among monozygotic (60%) compared with dizygotic (20%) indicating a genetic component to susceptibility.[21,22]

TB is a genetically primed and determined infectious disease caused by *M. tuberculosis*. The genetic polymorphism has been thought to be the mechanism that leads to progression from infection to TB disease.[20,21,22] Heritability has been explained on the basis of resistance to genetic susceptibility by a compromised immune response to a foreign pathogen to develop infection.

However, evidence suggests host biology and factors independent of host immunocompetence may dictate the emergence of tuberculosis.: not all *M. tuberculosis*-infected persons develop TB disease.[20,21,22] Also, Host biology explains why not all immune compromised and infected patients progress to TB disease and why not all patients with diabetes mellitus who are infected with *M. tuberculosis* develop TB.[20,21,22]

TB has a human origin

Biomolecular studies demonstrated that human TB has a human origin.[23]

M. Tuberculosis a long coevolution of the disease and its human host. The disease was present in the early human populations of Africa at least 70000 years ago and that it expanded following the migrations of Homo sapiens out of Africa, adapting to the different human groups.[23]

How did the first modern human develop tuberculosis?

He developed tuberculosis after being colonized by M. tuberculosis.

How did the first modern human get colonized by M. tuberculosis?

M. tuberculosis does not proliferate in the inanimate environment.[24] Traditionally, it was thought that TB has a zoonotic origin, being acquired by humans from cattle during the Neolithic revolution. However, the biomolecular studies demonstrated that human tuberculosis has a human origin.[23]

Host biology governs TB

It has been observed that not all immune compromised patients colonized with M. tuberculosis progress to tuberculosis.[20] Also, not all patients with diabetes colonized by M. tuberculosis develop tuberculosis.[20]

These observations suggest biological influences independent of immunocompetence may be of significance in the development of tuberculosis.

The accidental administration of live M. tuberculosis to babies in Lübeck, Germany in 1926 caused no disease in some but led to severe disease and death in others[25] suggesting that host biology determines tuberculosis.

In summary, host biology and factors independent of host immunocompetence seem to dictate the transformation of M. tuberculosis to a pathogen causing tuberculosis.

Immunodiagnostic tests can not distinguish tuberculosis disease from colonization- latent infection.[26]

Incidence of colonization changed despite successful tuberculosis treatment?

Number of people with normal flora and disease free) remains fixed despite dramatic drops in active tuberculosis.

RESULTS

The probability of human cells producing M. Tuberculosis is %99.999 (table A).

For the great majority of people, M. tuberculosis is part of normal human physiology and flora.

DISCUSSION

Host biology seems to dictate the transformation of M. tuberculosis to a pathogen causing tuberculosis. Of significance, not all immune compromised patients colonized with M. tuberculosis progress to tuberculosis and not all patients with diabetes colonized by M. tuberculosis develop tuberculosis suggesting that host biology and factors independent of host immunocompetence seem to determine the transformation of M. tuberculosis to a pathogen causing tuberculosis.

Noteworthy is the observation that the probability of human cells producing M. Tuberculosis is %99.999 (TABLE A)

At present it we do not know the biological processes involved in production of M. tuberculosis. It seems logical to consider that lung epithelial stem cells are the most likely candidates of origin.

Experimental studies are necessary to validate our findings.

Several aspects of this novel observation seem to be worthy of emphasis for they represent a paradigm shift in our understanding of and approach to various infectious disorders. They reveal complex dynamic processes involved in infectious disorders and endogenous pathways of microbial production from independent of foreign invading pathogens infecting humans.

CONCLUSION

M. tuberculosis is heritable.

For the great majority of people, M. tuberculosis is part of normal human physiology and flora produced by human cells. Host biology seems to dictate the transformation of M. tuberculosis to a pathogen causing tuberculosis.

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Observations consistent with M. Tuberculosis is heritable and may be produced independent of contamination

Odds of certainty=% 99.999

1. Normal flora, normal human physiology.
2. Fetus is not sterile without any evidence of contamination
3. Mycobacteria paratuberculosis is internally produced and inconsistent with contamination.
4. M. tuberculosis part of normal human physiology.
5. Tinea versicolor is an endogenous infection.
6. Pylori is an endogenous infection.
7. Myiasis is an endogenous infections.
8. Coevolved with humans.
9. Global distribution mimicking human migration.
10. Host biology- independent of immunocompetence-governs M. tuberculosis.
11. Humans are the predominant reservoir of M. tuberculosis.
12. Mycobacteria do not proliferate in the environment.
13. Immunodiagnostic tests cannot distinguish tuberculosis disease from colonization- latent infection.
14. Number of people with normal flora and disease free remains fixed.
15. Some human colonization may originate from host tissues and are not caused by contaminants from the environment.
16. Host Genetics shape gut microflora in mice.