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How can we keep kids from dying from diarrhea?

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Abstract

Many different bacteria, viruses and parasites can cause diarrhea. Sometimes diarrhea is just uncomfortable, sometimes it's deadly. In fact, in many countries in Africa and Asia, diarrhea is a major cause of death in children. If a child's diarrhea is caused by some types of bacteria, *Shigella* for instance, things can get pretty bad. *Shigella* is a leading cause of *morbidity* (the rate of disease in a population) and *mortality* (the number of deaths due to a disease) among children worldwide. Some countries don't have the ability to test for *Shigella*, so doctors rely only on symptoms to diagnose it and to see if antibiotic treatment is needed. We wanted to check if the method recommended by the World Health Organization (WHO) - looking for blood in children's stool - really identifies *Shigella*-infected children. We found that it doesn't - only a small proportion of children with *Shigella* had blood in their stool. We therefore recommend using a different method to determine which children with diarrhea need antibiotic treatment.

Introduction

Imagine you are blindfolded and you have to find an apple in a large pile of oranges and peaches – it would take a long time and you would probably make some mistakes. Doctors often face a similar problem when they have to diagnose a disease. Observing symptoms is rarely enough to make a definitive diagnosis. Although doctors can use diagnostic tests to aid in the detection of the disease, in many poorer countries, these tests are not always available or too expensive. In these settings, doctors are kind of "blindfolded" and have to only rely on the symptoms they observe. This is not ideal, as the same symptom can occur in a wide range of diseases. Diarrhea is one such example, and is caused by many different bacteria, viruses and parasites. Most diarrhea can be managed by making sure that children do not become dehydrated from loss of fluids. However, some forms of bacterial diarrhea do require antibiotic treatment.

Diarrhea is usually mild and passes quickly, but this is not always the case. *Shigella* bacteria (Fig. 1) can be life-threatening and is especially dangerous in resource-limited countries like Kenya.

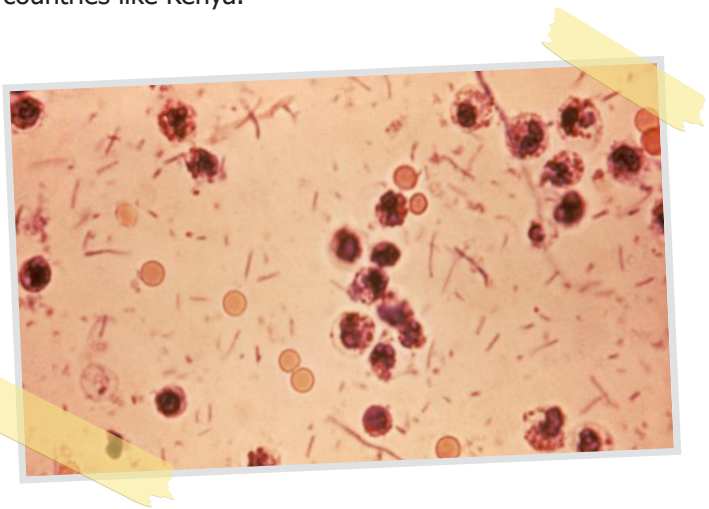

Figure 1:
Microscopic view of Shigella bacteria (thin pink rods) in a stool sample.

If doctors knew better who was infected by *Shigella* bacteria, they could save a lot more lives by treating these children with antibiotics. However, antibiotics can lead to *antibiotic resistance* if used in children without bacterial infections.

Without diagnostic tests, how do doctors know who has *Shigella* and who doesn't? The WHO recommends the use of a certain symptom – blood in the stool - to diagnose *Shigella* infections in children. We wanted to know if this method is *sensitive* and *specific* (the ability of a test to correctly identify the people with the disease and the ones without it) for this infection and to compare it with other characteristics to see if they work better for detecting *Shigella.*

Methods

We tested 1360 children from Kenya (aged 6 months to 5 years) with *acute diarrhea.* First, we asked their family about the children's history of disease and whether there had been any signs in the children other than diarrhea:

1. More dangerous signs - excessive vomiting, the child can't eat or drink, *convulsions*, (sudden irregular movements), a stiff neck or *lethargy*
2. Dehydration signs - sunken eyes, restlessness, thirst
3. *Dysentery* signs – blood in the stool

We then measured the children's weight and height which can show us whether the kids are lighter or smaller than average and potentially suffer from malnutrition. (Malnourished children are at increased risk of death from diarrhea.)

Finally, we collected stool samples from all children, and examined them for blood, mucus and texture (watery vs. solid). We put a small amount of the stool sample on a culture plate to see whether *Shigella* would grow (*bacteria culture test*). We looked for other bacteria by culturing the bacteria in their stool followed by using molecular detection methods (*polymerase chain reaction assays*) to see if we could find genetic evidence of pathogens known to cause disease. We also examined the stool sample with the microscope to check for parasites. Finally, we collected blood samples from the children to determine if they had HIV (Human Immunodeficiency Virus).

We tested the specificity and sensitivity of the symptom-based detection of *Shigella* and compared it with four other sets of characteristics:

- Model 1: (recommended by WHO): dysentery (blood in stool)
- Model 2: Model 1 + observed mucus or watery stool
- Model 3: Model 2 + danger signs and dehydration signs, fever
- Model 4: Model 3 + weight and height ratios
- Model 5: Model 4 + HIV and Malaria results

Results

What did we find out after talking to the families of all 1360 children, measuring the kids' weight and height and examining their stool and blood samples? See for yourself in Table 1.

Table 2 shows what we found out specifically about the children who had *Shigella* (*Shigella* positive) and the ones who didn't (S*higella* negative).

With this information, we calculated the *sensitivity* (11%) and *specificity* (94%) of the WHO-recommended model for *Shigella* detection – visible blood in stool. Our proposed models showed slightly improved results but not as good as we hoped.

Please, see Table 1 and Table 2 on Page 3

Observed signs and symptoms in children	Numbers reported	Numbers positive	Percent positive
Dangerous signs	1360	396	29%
Dehydration signs	1360	188	14%
Severe dehydration	1360	81	6%
Reported bloody stool	1213	79	7%
Lower height	1360	220	16%
Lower weight	1360	243	18%
Additional medical tests	**Numbers reported**	**Numbers positive**	**Percent positive**
Blood in stool	1247	15	1%
Mucus in stool	1247	696	56%
Watery stool	1247	863	69%
Shigella	1360	63	5%
Parasites	1247	228	18%
HIV	1360	46	3%

Table 1:
Data collected from 1360 children in Kenya.

How many children have *Shigella*?

How many children who have *Shigella* had blood in their stool?

Characteristic	Shigella positive (%)	Shigella negative (%)
Age below 2 years	19 (30%)	731 (56%)
Age 2-5 years	44 (70%)	566 (44%)
Dangerous signs	11 (18%)	412 (32%)
No dehydration	52 (83%)	1039 (80%)
Some dehydration	8 (13%)	180 (14%)
Severe dehydration	2 (5%)	8 (6%)
Blood in stool	**2 (3%)**	**13 (1%)**
Reported bloody stool	**7 (13%)**	**72 (6%)**
Mucus in stool	42 (67%)	654 (50%)
Lower height	7 (11%)	213 (17%)
Lower weight	8 (13%)	235 (18%)
Malaria	4 (6%)	139 (11%)
HIV	3 (5%)	43 (3%)
Shigella positive total 63; Shigella negative total 1297		

Table 2:
Comparison between children with *Shigella* (positive) and those without *Shigella* (negative).

Discussion

Our study showed that the model recommended by WHO has its limitations. If doctors used dysentery (bloody stool) as the only indicator for *Shigella* infection, they would have missed a lot of sick children who might benefit from antibiotic treatment. WHO recommends checking for bloody stool in order to detect *Shigella* because until recently, *Shigella dysenteriae* type I (which usually causes blood in stool) used to be the most dangerous *Shigella* species. Now there is evidence that two other species may cause as much death, are more widespread, and are less likely to cause dysentery (hence the low sensitivity).

In this study we identified other factors, such as presence of mucus, age over 2 years and absence of excessive vomiting, which could help find out whether children have been infected with *Shigella* or not. But the sensitivity of our new proposed models is still not good enough to reliably detect *Shigella* infection every time. In addition, using different criteria based on our models might also lead to antibiotic treatment of a lot of children not infected with *Shigella*, which could result in more antibiotic resistance.

Conclusion

We recommend reconsidering dysentery as the sole indicator for *Shigella* infections. Ideally an inexpensive test to detect *Shigella* infection that provides results within a few minutes could be developed and used to guide treatment.

It is also important to remember that children are infected with *Shigella* and many other similar bacteria and viruses (including Hepatitis A) via the so-called fecal-oral route. This sounds pretty bad but the good news is that you can usually prevent these infections with simple measures like always washing your hands before eating and after using the bathroom!

Glossary of Key Terms

Acute diarrhea – three or more abnormally loose or watery stools within the past 24 hours lasting less than 14 days.

Antibiotics – a type of medication that treat or prevent bacterial infections by either killing or preventing the growth of the bacteria.

Antibiotic resistance – occurs when bacteria change in a way that reduces the effectiveness of drugs or chemicals designed to cure or prevent infections. The bacteria survive and continue to multiply, causing more harm.

Bacterial culture test (also called microbiological isolation) – a test that is performed by taking sterile swabs or samples from an area of the body which is infected, then placing these samples in a specific medium which helps certain bacteria to grow. If there is bacterial growth, scientist can see which bacteria the patient has.

Convulsion – a sudden, violent, irregular movement of a limb or of the body.

Dysentery – infection of the intestines, causes blood in stool.

Lethargy – a lack of energy and enthusiasm.

Morbidity – a term describing how often a disease occurs (in an area or population), for example, the number of people in your country who have cancer.

Mortality – deaths due to a disease. For example, 50 out of 10,000 people die of diabetes. The mortality rate is 5:1000.

Polymerase Chain Reaction – a technique used in molecular biology to multiply DNA, generating thousands to millions of copies of a particular DNA sequence.

Sensitivity of a test – tells us how often a test for a specific disease will be positive (true positive rate) if a person has the disease of interest. The formula is pretty easy: TP/ (TP + FN), where: TP - true positive (your correct positive results); FN - false negative (your incorrect negative results). Example: out of 100 positive, your test results show 80 positive. You have 80 TP, and 20 FN. So the sensitivity is 80%.

Shigella – a genus of bacteria, related to *E.coli,* causing mild to severe diarrhea. There are different species of *Shigella (S. dysenteriae, S. flexneri, S. boydii, S. sonnei)* and the disease they cause is called shigellosis. Symptoms of shigellosis include diarrhea, fever, abdominal pain and sometimes blood in the stool.

Specificity of a test – tells us if a person doesn't have a disease, how often will the test for it be negative (true negative rate). The formula is: TN/(TN+FP), where: TN - true negative (your correct negative results); FP - false positive (your incorrect positive results). Example: out of 100 negative, your test results show 91 negative. You have 91 TN and 9FP. So the specificity is 91%.

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Mayo Clinic: Information on *Shigella* symptoms, causes, diagnosis and treatment
https://www.mayoclinic.org/diseases-conditions/shigella/symptoms-causes/syc-20377529

WebMD: What does your stool say about you?
https://www.webmd.com/digestive-disorders/ss/slideshow-poop-type-color

Check your understanding

1 Why don't doctors just give antibiotics to every child with diarrhea?

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2 You invented a new test method for detection of Cholera, a dangerous bacterial disease. You correctly recognized 95 out of 100 positive samples and out of 100 negative samples you wrongly found 1 positive. What is your new test sensitivity? And specificity?

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3 A tick bit you and you did a Lyme disease laboratory test. It turned out negative but then you see the test's sensitivity is 60%, what does this mean?

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4 Sometimes you can catch bacteria and viruses, transmitted through the fecal-oral route even when you wash your hands. Why?
