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Helicobacter pylori infection in children in the Tyva Republic (Russia)

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Keywords:	Helicobacter pylori, prevalence, children

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Helicobacter pylori infection in children in the Tyva Republic (Russia)

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Keywords: *Helicobacter pylori*, children, Central Asia, family, prevalence

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For Review Only

ABSTRACT:

Background: Tyva Republic is a small mountainous area at the geographical center of Asia in southern Siberia. With a high incidence of gastric cancer. **Aim:** We examined the prevalence of *H. pylori* and associated risk factors among children in Tyva. **Methods:** Cross-sectional study was conducted among Tuvan children who had upper gastrointestinal symptoms and underwent upper gastroscopy with gastric biopsies. Informed consent was obtained from the parents and assent from the children. Demographic information, ethnicity; parents' education and employment status and family size were collected. *H. pylori* infection was diagnosed by histologic examination. **Results:** There were 270 children between the ages 7 and 17 years (mean 13.4 ± 2.7); 64% girls; 147e Tuvan and 123 Caucasians. The overall prevalence of *H. pylori* was high and similar between boys and girls (55 vs 57%, respectively, $p = 0.42$). The infection was highest Tuvan children (67%. vs 43%, respectively (OR=2.4; 95%CI=1.9.4-3), $p=0.0.005$. *H. pylori* prevalence increased with age from 44% among 7 to 10 years and 64% among those 14 to 17 (OR=3.0; 95%CI=1.6-5.8), $p=0.0.005$; the pattern was consistent among both ethnic groups. The prevalence of the infection among Caucasian children was inversely correlated with the level of mother's education (44%, vs. 61%) (i.e., for with and without a college education the OR=2.3; 95%CI=1.2-3.7), $p=0.02$. Neither the total number of children nor adults living in the same household correlated with *H. pylori* prevalence. **Conclusions:** Strategies of reduce the incidence of gastric cancer in Tyva will need to start in childhood.

INTRODUCTION:

Helicobacter pylori (*H. pylori*) infection is etiologically related to gastritis and its associated diseases such as gastric cancer and peptic ulcer, (1-4). Gastric cancer is the third leading cause of cancer-related death in the world and its risk varies among the countries and populations (5). In 1994, the International Agency for Research on Cancer categorized *H. pylori* infection as a definite group I carcinogen (6). Childhood is critically important in the acquisition of infection (7-11). In developing nations, the majority of children are infected before the age of 10 (7). The prevalence of *H. pylori* infection varies both among and within populations and is inversely related to standards of living and hygiene and sanitation (8-11). The risk of acquisition of the infection is especially high among those living in developing countries (12-15).

The prevalence of *H. pylori* infection varies among the different populations that make up Russia (16-18). The Russian Republic of Tyva is located in the center of Asia and shares the border with Mongolia in the south. While Tyva has a high incidence of gastric cancer, especially among the Mongoloid population, the epidemiology of *H. pylori* infection among children has not been investigated. Therefore, we conducted the current study to examine the epidemiology of *H. pylori* and associated risk factors among children in Tyva.

2. MATERIAL AND METHODS

Population: The study was carried out in settlements within the Republic of Tyva (Russian Federation, Siberia). The population of the Republic is approximately 325,000. The dominant population (80%) is indigenous Mongoloids; the remaining are Caucasians (Russians, Ukrainians, Belarusians) with about 1% being the indigenous inhabitants of Siberia [20, 21].

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3 **Geography and climate:** The Republic of Tyva is located in the center of Asia; south of Eastern
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5 Siberia. Kyzyl is the capital city (Figure 1). The climate in Tyva varies based on the elevation as
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7 the high mountains dictate the local climate and isolate the region from the impact of climate
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9 conditions externally. The temperature in the winter is -30 to -50 C and while in the summer rises
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11 to 35-45 C.
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14 **Study Design:** The study was carried out between 2017 and 2019 by a team from the Scientific
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16 Research Institute of the North of the Federal Research Center of the Siberian Branch. It involved
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18 the villages of the Tyva Republic (Saryg-Sep and Turan) which represent the Tyva population.
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20 The study involved two stages: the first was a cross-sectional study conducted to screen children
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22 to identify those with gastroenterological complaints. A standardized questionnaire was
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24 completed by each student and parent under the supervision of member of the research team. The
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26 data collected included upper gastrointestinal symptoms, demographics, social characteristics of
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28 the family, education and employment status of the parents and the number of children in the
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30 family. Only for children age 7 to 17 inclusive were invited to participate in the study with
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32 parental consent.
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38 The second stage involved the children with upper gastrointestinal symptoms identified in the
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40 first stage. Each underwent upper endoscopy with biopsies were taken from the antrum and
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42 Vitaliy Alekseevich Vshivkov greater curvature of the corpus. All upper endoscopies were
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44 carried out by a single doctor to standardize the biopsy sites. The criteria for children to be
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46 included were the presence of gastroenterological complaints in the absence of acute
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48 inflammatory disorder, chronic disease, or functional failure of any organ. In accordance with the
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50 World Medical Association (WMA) Declaration of Helsinki governing scientific research. All
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52 participants over 15 years of age and parents/legal guardians of provided informed consent prior
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3 to inclusion in the study. The informed consent form and the research plan were reviewed and
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5 approved by the Ethics Committee of FSBI «Federal Research Center", Krasnoyarsk Science
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7 Center of the Siberian Branch of the Russian Academy of Sciences» - the Research Institute for
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9 Medical Problems in the North, Krasnoyarsk (February 13, 2017; approval no. 2).

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12 **Histologic Examination:** All biopsies were fixed in 10% neutral-buffered formalin and
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14 embedded in paraffin blocks. Sections were stained with Giemsa stain to evaluate for *H. pylori*.
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16 The morphological changes in the gastric mucosa were classified according to the updated
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18 Sydney classification [25, 26].
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22 **Statistical Analysis:** The statistical processing of the results was carried out using the SPSS
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24 version 23.0 software (IBM, Inc.). The statistical significance of differences in qualitative
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26 characters was analyzed by the Pearson chi-square test. The relative risk of various factors
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28 influencing *H. pylori* infection was calculated by logistic regression analysis using odds ratio
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30 (OR) and 95% confidence interval (CI). Multiple regression analyses were adjusted for gender
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32 and the age group. The critical level of significance when testing statistical hypotheses was taken
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34 to be equal to 0.05.
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40 **3. RESULTS:**

41 **Prevalence of *H. pylori* infection among children in Tyva:**

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43 A total of 270 children between the ages 7 and 17 years (mean 13.4 ± 3); 64% girls including
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45 147 Tuvans and 123 Caucasians participated in the study. The overall prevalence of *H. pylori*
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47 was 56% with no difference between boys and girls (55 vs 57%, respectively, $p = 0.42$). There
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49 was a significant difference in prevalence between Tuvan and Caucasian children; (67% vs.
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51 43%; respectively, $p = 0.001$) (Fig-2; Table-1).
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***H. pylori* positivity and demographic, geographic, and environmental variables:**

The prevalence of *H. pylori* infection increased with age among and among Tuvan and Caucasian children independently (Fig-3). The youngest Tuvan children (between the age of 7 and 10 years) had a two times higher prevalence of the infection similar age Caucasians children (58% vs. 27%, respectively, (OR=2.3; 95%CI=1.6-3.7), p=0001. Among all the children studied the *H. pylori* prevalence was inversely correlated with the level of mother's education (i.e., those did not complete secondary school vs. university education); 61%, vs. 44%; respectively, p=0.05. This trend was only significant among the Caucasians subjects (Fig-4) and did not extend to the father's education (Table-1).

The prevalence of *H. pylori* infection was examined in relation to the number of children living within households and whether they also cohabitated with an older generation (e.g., grandparents). Neither the total number of children nor the proportion living with grandparents correlated with *H. pylori* prevalence (Table-1) for either ethnic group. When logistic regression analysis was applied with all the variables in the model, ethnicity, age and mother education were the variables emerged at a significant level.

DISCUSSION

To our knowledge this is the first study to report on the epidemiology of *H. pylori* among children in the Republic of Tyva, a country with high stomach cancer morbidity (19). One of the marked finding of the study is the high prevalence of *H. pylori* infection among children and the significant difference in *H. pylori* prevalence based on ethnicity (i.e., Tuvan children also had

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3 significant higher *H. pylori* prevalence than Caucasian children which is consistent with the
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5 higher morbidity from gastric cancer among Tuvans.
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8 It is accepted that much of the variation in the prevalence and acquisition of infection among
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10 ethnic and racial groups is primarily related to differential exposure such in cultural background,
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12 social, dietary and environmental factors (8-13) with little evidence of a difference in genetic
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14 predisposition (20). The high prevalence of *H. pylori* among the Tuvan children is almost
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16 identical to that of Mongolian children residing in neighbouring Mongolia who have the same
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18 ethnic background and high rate of gastric cancer (21). It is reported that the prevalence of *H.*
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20 *pylori* infection in Mongolia is as high as 80% among adults (22-23), and 65% and 100% among
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22 adolescents and pediatric patients, respectively and associated with high gastric comorbidity
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24 (24). The high prevalence of *H. pylori* in the current study is comparable to what is reported in
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26 other developing countries (9-14) which has been interpreted to be a marker of a relatively lower
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28 level of sanitation and household hygienic (25).
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33 Another novel finding of this study is the markedly higher prevalence of *H. pylori* among the
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35 youngest Tuvan children and emphasizes the importance of the acquisition before the age of 10
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37 years (7). Moreover, the prevalence of the infection continued to increase with age among
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39 children and that the increase was consistency in each ethnic group independently. Prior cross-
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41 sectional studies have consistently shown a gradual increase in *H. pylori* prevalence with age
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43 which has been interpreted as a birth cohort effect that reflects the decrease in the rate of
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45 acquisition in successive generations of children as sanitation and standards of living improved
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47 (8;26-28). While globally there is a wide range of the prevalence of the infection among children
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49 (8-14), the overall prevalence of the infection among the native Tuvan children appears to be one
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51 of the highest prevalence in the world today. For example, recent studies report the prevalence of
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3 *H. pylori* infection among Chinese children as 6.8% (29), 33% in a Portuguese pediatric
4 population (30), 5% among junior high school students in Japan (31), 42% among children in
5 Iran (23), and 36% of in hospital-based cohort of children in Nepal (33). While it has been also
6 established that the prevalence of *H. pylori* is inversely related to socioeconomic status, for
7 populations in which the social class is relatively homogeneous, such as in Russia and,
8 particularly the Republic of Tyva, the level of mothers' education proved to be an important
9 variable and is also a likely marker for the sanitary level of the household. Moreover, in the
10 majority of the Russian families, mothers traditionally take most of responsibilities of their
11 household duties. Although, the prevalence of *H. pylori* infection was inversely correlated with
12 the level of mother's education, the trend was only statistically significant among Caucasians
13 likely because although both Tuvans and Caucasians reside within the same country, each
14 maintains their unique backgrounds, histories, and cultural characteristics that likely contribute
15 to difference in the prevalence of the infection among the different ethnic groups. Among the
16 factors reported to affect the incidence of *H. pylori* infection in children is the density or number
17 of people within the home. Interestingly, we did not find a significant impact based on the
18 number of sibling nor living with an older generation in the same household.

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40 In conclusion, the prevalence of *H. pylori* among children in Tyva is very high among specially
41 among native Tuvans. Any gastric cancer prevention strategy will need to consider the effect of
42 early acquisition of the infection in children in the Republic of Tyva.
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TABLE-1: Distribution of *H. pylori* infection by the study variables in Tuvan children

Variable	Total (+ve <i>Hp</i> %)	Crude OR 95% CI	Age Adjusted OR 95% CI
Age:			
7-10	62 (44%)	Ref	
11-13	88 (53%)	1.5 (0.8-2.8)	
14-17	120 (64%)	2.5 (1.3-4.4)**	
Total	270 (56%)		
Gender:			
Boys	97 (55%)	Ref	Ref
Girls	173 (57%)	1.2 (0.6-2.6)	1.0 (0.5-3.1)
Ethnicity:			
Caucasians	123 (43%)	Ref	Ref
Tuvans	147 (67%)	2.4 (1.9-4.6)**	2.0 (1.4-3.6)**
Mother's ED*:			
University	52 (44%)	Ref	Ref
Secondary Vocational	75 (53%)	1.7 (0.9-2.0)	1.1 (0.5-2.1)
Incomplete Secondary	54 (58%)	2.0 (1.2-4.1)*	1.9 (0.98-3.23)**
Missing	89		
Father's ED*:			
University	29 (52%)	Ref	Ref
Secondary Vocational	55 (53%)	1.1 (0.4-4.8)	1.0 (0.3-2.2)
Incomplete Secondary	97 (58%)	1.3 (0.6-3.4)	1.0 (0.4-4.0)
Missing	89		
# of children in the household:			
1	36 (53%)	Ref	Ref
2	74 (51%)	1.1 (0.5-2.4)	0.9 (0.4-3.0)
≥3	71 (61%)	1.4 (0.7-3.1)	1.1 (0.3-3.4)
Missing	89		
# Living with grandparent (S)			
Yes	23 (65%)	Ref	Ref
No	158 (54%)	1.6 (0.7-4.1)	1.2 (0.7-2.9)
Missing	89		

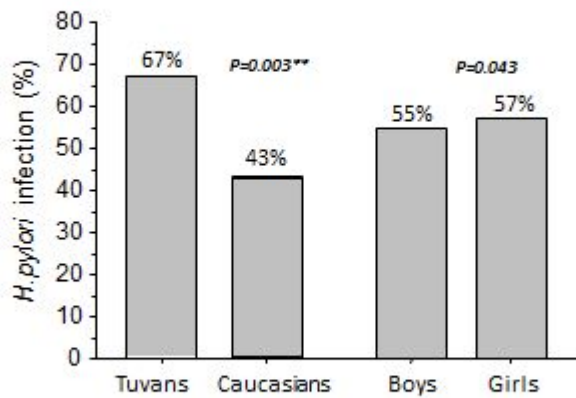
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Fig-1

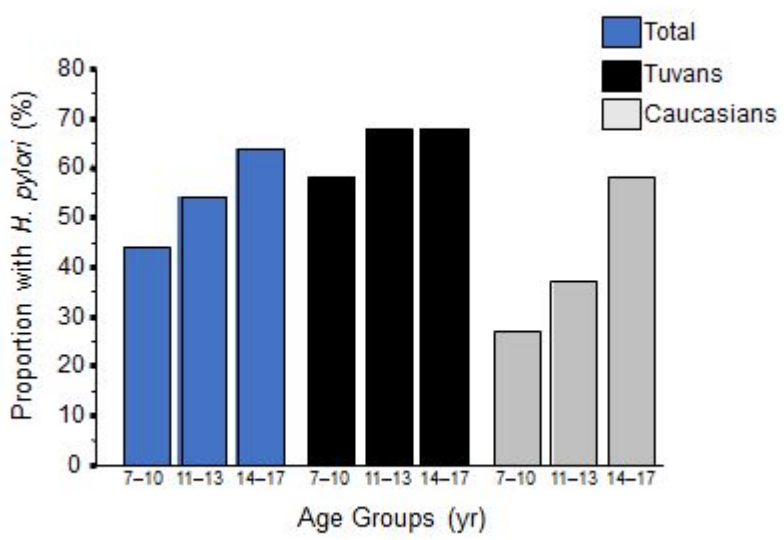


Fig-2



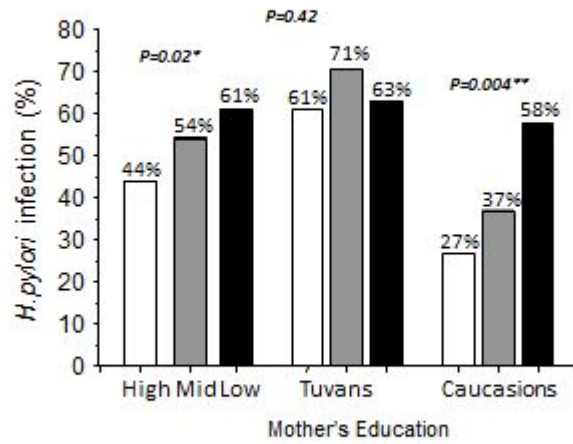
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14 Dear Editor
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17 Thank you for reconsidering to review our manuscript “Epidemiology *Helicobacter pylori*
18 infection in children in the Tyva Republic (Russia). We highlighted our responses easier track
19 throughout the text.
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25 **In response to the reviewer:**
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28 1. Prevalence *H. pylori* has been widely studied, including in areas with a high incidence of
29 gastric cancer (kindly check the article PMID: 26931643), moderate (kindly check the
30 article PMID: 26226153), and low (kindly check the article PMID: 26599790), therefore
31 it is necessary to write in the introduction, the main reasons why it is necessary to study
32 the prevalence in Tyva Republic, hence the readers will be able to relate phenomena in
33 this area to other countries. **We responded adequately to the reviewer’s comment,**
34 **modified a paragraph in the introduction and added the recommended references.**
35 ..
36 2. The method should be written in detail, for example, how many cm is the distance from
37 the pylorus when taking a biopsy from the antrum? Who does the endoscopists and
38 pathologist and their experiences in this field? (write the initial name xx)
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41 **Per Professor Vitaliy Alekseevich Vshivkov, the lead author of the project, he was**
42 **the only endoscopist who performed all endoscopies on children and there is only**
43 **one pathologist who read all the slides. That did not allow any biased in performing**
44 **of taking biopsies or reading the slides.**
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47 3. **As for the sample size calculation issue raised by the reviewer. There was a**
48 **calculation for the largest survey that started with screenings and examining**
49 examined 1535 subjects totally. The criteria for choosing children of the current research
50 were based on children between the ages of 7 to 17 years from either ethnic group;
51 Tyvinians or Europoids.
52 Then, out of the total screening cohort of schoolchildren, the authors randomly selected
53 the current studied children.
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4. Do the authors have data on the prevalence of *H. pylori* in adults in Tyva Republic therefore the authors could compare it with data on children in this study.
I am certain that our Tayvion colleagues have data to be published on *H. pylori* in adults. However, our current study is focusing on the epidemiology of the infection among children as it is known childhood is the major risk of acquisition of the infection.
5. The authors should determine the interesting risk factors in this study, for example, mother's education has significant correlation. This should be the main focus of manuscript writing, therefore it is not focused only on the prevalence. Which ended up having to change the title and overall discussion.
We disagree with the reviewer about the point of changing the scope of the study and focus on mother's education. Our focus in the current study was on the epidemiology of all the risk variables that could be associated with the infection. Moreover, the mothers' education emerged as risk factor among the Caucasian group only. We strongly believe the current study should not focus on one single risk factor.

26 We hope we have responded adequately to the reviewers' comments and the manuscript is now
27 acceptable for publication in your journal.
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29 Sincerely
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33 Hoda M. Malaty, M.D., Ph.D.
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