STUDY PROTOCOL

Official Title of the study:

«Seroprevalence of Pertussis among Healthy Children and Adolescents in Kazakhstan: A Cross-Sectional Study»

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Scientific organization: **Scientific and practical centre of sanitary and epidemiological expertise and monitoring, Almaty, Kazakhstan**

Contents

1 Synopsis

Study Sponsor	Scientific and practical centre of sanitary and epidemiological expertise and monitoring
Title of the study	Seroprevalence of pertussis among older children and adolescents in Kazakhstan: A cross sectional study
Vaccines or disease area	Pertussis - Whooping cough
Planned study period	January 2021 - October 2021
Background and rationale	Pertussis due to infection with Bordetella pertussis (B pertussis) is a well-known cause of persistent cough primarily affecting infants and young children. Repeated administration of the vaccine is often needed to reduce the disease burden and control its transmission. At this time, no data are available on the epidemiology of pertussis in adolescents and adults in Kazakhstan. The aim of the present study is to estimate the prevalence of pertussis infection in different age groups in Kazakh children and adolescents using the anti-pertussis toxin (PT) antibodies (IgA and IgG) as specific marker of pertussis infection or vaccination. The serosurvey will be conducted in 4 different regions: Aktobe, Karaganda, Taldykorgan, and Shymkent.
Objectives	Primary Objective: To describe the distribution of anti-pertussis toxin (PT) antibodies (IgA and IgG) in a population aged 10-18 years old according to sociodemographic characteristics, vaccination history, and risk factors of pertussis infection.
Study design	Cross-sectional
Inclusion and exclusion criteria	**Inclusion criteria:** 10-18 years old • Informed consent obtained from parents or guardian(s) and assent from patient. • Enrollment following a visit at the study center. • Documented vaccination history **Exclusion criteria:** • ≤10 years and ≥ 19 years • Pertussis immunization during the last 12 months • No informed consent obtained from one parent or guardian.

	• Immunocompromised patients • Patients with acute infectious diseases
Study procedures	Participants (≥ 10 years & < 19 years) attending the study centres will be asked to participate in the study. The adolescent participants and the parents/guardian(s) of all participants will be informed about the procedures and data handling. Written informed consent from one parent/guardian needs to be obtained by the physician before any blood samples can be taken. Upon obtaining informed consent for participant parent/guardian, the study coordinator will complete an investigation form (IF) for each participant and collect serum samples. The specimens will be coded by a unique participant number and delivered to the laboratory in charge of the assay. The specimens will be used for serological analyses. The study will be approved by the Ethics Committee of the Scientific and practical centre of sanitary and epidemiological expertise and monitoring.
Monitoring procedures:	Completed IFs, Informed Consent Forms, copies of laboratory and clinical data will be stored in the study center. Each IF will be coded with a unique identification code. The study team will check the IFs for completeness and consistency and resolve queries.
Data analysis	The mean of antibodies of antiPT will be described and variability measurements (standard deviation and inter quartile range). The seroprevalence of pertussis will be described using proportions. Correlation between IgG and IgA levels and risk factors will be analyzed by multivariable regression. A two-tailed P-value of ≤ 0.05 will be considered for statistical significance.
Study report and communication plan	An intermediary and final reports will be prepared summarizing the study results. The results will also be published in an (inter)national conference and in a peer-reviewed journal.

List of abbreviations

Bp	Bordetella pertussis
°C	Degrees Celsius
CI	Confidence Interval
DTP	Diphtheria, tetanus, pertussis vaccine
ELISA	Enzyme-linked immunosorbent assay
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
PCR	Polymerase Chain Reaction
PT	Pertussis Toxin
SD	Standard Deviation
Tdap	Tetanus, diphtheria, acellular pertussis vaccine

1. Introduction

Pertussis infection with Bordetella pertussis (Bp) is a well-known cause of persistent cough primarily affecting infants and young children. Pertussis immunization programs designed to protect infants and young children resulted in a dramatic decline of pertussis incidence but not in its elimination [1,2]. Endemicity of the disease is due to waning of immunity against pertussis of vaccinated population either with whole cell or acellular pertussis vaccines [3]. The absence of repeated boosting of the protective immunity is known to cause an increase of the risk of infection and increased transmission to unprotected infants [4–6]. In Kazakhstan, the childhood routine vaccination covers children until the age of 6 years old with a schedule containing the primary series and two booster doses at 18 months and 6 years old. Adolescents receive a booster dose of tetanus and diphtheria only without pertussis. It has been shown that pertussis is circulating among adolescents and adults, which contributes to the overall burden, and importantly furthers the transmission dynamic of the disease to other age groups.

Currently, little data are available on the epidemiology of pertussis beyond the pediatric population in Kazakhstan. Risk of pertussis infection may be assessed to justify the need of repeated booster in the appropriate age among adolescents.

Population-based or cross-sectional sero-epidemiology studies offer an appropriate approach to estimating a proxy of the risk of pertussis infection [9,10]. Sero-survey studies, using a standardized and reproducible serological test measuring the IgG and IgA pertussis toxin by ELISA, give an estimate of recent infection specific to Bordetella pertussis.

Data using standardized methods to assess the serum anti-PT IgG and IgA levels are currently available in several developing and developed countries providing means of estimating the prevalence of recent infection in the targeted population [8,10–16]. These estimates are dependent on the calculated cut-offs used to define recent exposure. Using these prevalence estimates and mathematical models, annual sero-incidences can be extrapolated to assess the risk of pertussis infection, and results [16].

2. Study goals and objectives

The aim of the present study is to estimate the seroprevalence of pertussis infection in a population aged 10-18 years old in the cities of Aktobe, Karaganda, Taldykorgan, and Shymkent using the anti-PT IgG and IgA antibodies as specific marker of pertussis infection or vaccination in children and young adolescent.

Primary Objective

- To estimate the prevalence of recent infection Bp infection, using increased anti-PT antibody levels as markers of Bp infection in the serology test.

Secondary Objectives

- To evaluate the risk factors associated with higher seroprevalence of pertussis.

Exploratory objectives

- To evaluate the compliance with recommended vaccination schedule in study participants

3. Outcomes

- The anti-PT IgG and Ig A concentrations (in IU/ml) in the population sample.
- The prevalence of recent Bp infection in the test in the selected population sample stratified by demographic and socio-economic criteria, vaccination history, and risk of infection.
- Adherence to vaccination status defined as the. number and timeliness of doses received and potential exposure to booster vaccination as well as the concordance with the Kazakh vaccination status

4. Study design and methodology

4.1. Study design and setting

This study will be a cross-sectional serosurvey of anti-PT levels in a sample of the population. The study will be conducted in the cities of Aktobe, Karaganda, Taldykorgan, and Shymkent. Enrolment will be done in health centres and paediatric hospitals.

4.2. Study population

Participants will be children and adolescents from 10 to 18 years of age, recruited from health centers and pediatric hospitals.

Inclusion criteria

The inclusion criteria for the population sample are:

- Age ≥ 10 years and < 19 years.
- Informed consent obtained from parents or guardian(s) and assent from patient.
- Enrollment following a visit at the study center.
- Documented vaccination history

Exclusion criteria

Potential study participants will be not eligible for inclusion in the study according to the following criteria:

- Patient age less than 10 years or greater than 19 years old.

- No informed consent obtained from parent or guardian
- More than five doses of pertussis vaccination in vaccination history.
- Institutionalized children
- Immunocompromised patients
- Patients with acute infectious diseases

Missing information

Patients with missing information will be excluded from the main analysis

- Missing information on the vaccine status (type of vaccine, number of doses and age of immunization)
- Missing relevant medical information
- Missing laboratory results

The characteristics of individuals with missing key information will be compared to included study population.

4.3. Sample size considerations

In this study, the target sample size is 554 participants to see a prevalence of 10% ± 5% in 4 different regions, Box 1.

Sample Size for Frequency in a Population

Population size(for finite population correction factor or fpc)(*N*):	1000000
Hypothesized % frequency of outcome factor in the population (*p*):	10%+/-5
Confidence limits as % of 100(absolute +/- %)(*d*):	5%
Design effect (for cluster surveys-*DEFF*):	4

Sample Size(*n*) for Various Confidence Levels

ConfidenceLevel(%)	Sample Size
95%	554
80%	237
90%	390
97%	679
99%	956
99.9%	1559
99.99%	2180

Equation

Sample size $n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$

Results from OpenEpi, Version 3, open source calculator--SSPropor

Print from the browser with ctrl-P

or select text to copy and paste to other programs.

Box. 1 Sample size calculation (OpenEpi®: Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06)

5. Study procedures

5.1. Study Sites

For this study, we will choose the main directorates in the cities of Kazakhstan (Aktobe, Karaganda, Taldykorgan, and Shymkent).

- For each directorate 4 pediatric hospitals and 8 policlinics.
- From each hospital 50 samples will be taken (each age for 10 samples).
- From each policlinic, 40 samples will be taken (each age for 10 samples).
- Total 520 samples in age from 10 to 18 will be taken during the study.

The table below shows more clearly the sample size that will be taken.

Table 1. Site name and sample size

Site name	Location	Age coverage	Sample size	Comment
4 Pediatric Hospitals	1 pediatric hospital in each city (Total: 4 hospitals)	10-14 years	200 samples (50 samples from each hospital)	In each hospital 10 samples from each age (10, 11, 12, 13, 14 y)
8 Health Centers	2 policlinics in each city (Total: 8 policlinics)	15-18 years	320 samples (40 samples from each policlinic)	In each policlinic 10 samples from each age (15, 16, 17, 18 y)
Total:	12 sites	10-18 years	520 samples	~60 samples in each age (10, 11, 12, 13, 14,15,16,17,18 y)

5.2. Specimen and Data collection

After receiving of an informed consent from the child's legal representative, the study coordinator (HCP) in the medical organizations will take a blood sample by venipuncture – approximately 3-5 ml of whole blood. Blood samples will be sent to the laboratories of the National Centers of Expertise, Control and safety of goods and services (cities Aktobe, Karaganda, Taldykorgan, Shymkent). Serum separation will be done within 24-48 hours of blood collection. The samples will be transferred to the reference laboratory of Scientific-Practical Center of Sanitary-Epidemiological Expertise and Monitoring (NPC SEEM) in Almaty, Kazakhstan. Samples will be delivered within one week in a frozen form following the cold chains requirements. Serum samples will be stored in the reference laboratory at a temperature of -20^{o} C.

Simultaneously with collecting the biological sample, the study coordinator will fill the IF to collect the demographic, socioeconomic, and clinical characteristics of each participant.

The following list of variables must be collected for all participants unless refusal to provide the information by the participant or the parent or guardian

Demographics	Household information	Clinical history*	Risk factors*	Vaccination status
Age Sex Residence Hospital or health center	Sick sibling or parent in household Confirmed diagnosis of parents	Suspected cases Cough, wheezing, cyanosis, and vomiting	Passive cigarette exposure Other recent or chronic respiratory disease Recent antibiotic use (past month) Other chronic or medical condition	Participant vaccination history Household vaccination history

The study coordinator will also enter the vaccination history in the investigation form based on participant vaccination registry/record. In absence of vaccination registry or record, parents or guardians of the participating individual will be asked on the vaccination status.
The study coordinator will collect a blood sample and assign the study code.

5.3. Monitoring procedures

All members of the study center involved in the study, will attend a training session at the study center, led by the study team. Training will include study procedures and methods of data collection. During the training session, they will receive a study start-up kit including study information (i.e., protocol, investigation form, informed consent forms and other study forms or study manuals/guidelines). Investigation forms will be coded with the participant unique study number. Every investigation form will be labeled with the same identification code as for the biological samples and checked for completeness and consistency. Each investigation form will be stored at NPC CEEM of MoH in Kazakhstan. Likewise, the informed consent forms of the study participants will be also stored at NPC CEEM of MoH in Kazakhstan. All forms will be stored in a locked cabinet. Only study team members will have direct access to these forms.

5.4. Data handling

Each focal site and laboratory will return the resolved and signed IFs to the study team. Data entry will be performed centrally by the study team into a relational database specifically designed for the study. In the study database, participant data from the investigation form and laboratory results will be stored for each participant using the same participant identifier.

6. Laboratory methods

Pertussis antibody testing will be conducted at the Reference Laboratory in NPC CEEM of MoH in Kazakhstan. This laboratory is a member of the regional laboratories network for diagnosis of polio, measles, rubella and influenza. The Laboratory is accredited by the WHO for microbiology research and participates in external quality assessment programs with the WHO collaborating centers for ELISA and molecular genetic methods.

6.1. Laboratory procedure

In order to describe the distribution of anti PT antibodies, serum samples will be taken and tested for antibodies to pertussis toxin (PT) by enzyme-linked immunoassay (ELISA) using the SAVYON SeroPertussisTM kits (Savyon Diagnostics Ltd, Israel).

6.2. Cut-off definition.

Cut-off: According to recent literature and recommendations from reference laboratories across the EU, Savyon Diagnostics recommends the following interpretation of results for IgG concentrations:

IgG IU/ml	IU/ml	Result Interpretation
<40 IU/ml	Negative	No indication for an acute Infection
≥ 40 to <100 IU/ml	Intermediate	Possible infection; re-test IgG in 2-4 weeks or test for IgA levels
≥ 100 IU/ml	Positive	Indication for an acute infection or recent contact (in absence of recent vaccination)

IgA Cut-off: According to recent literature and recommendations from reference laboratories across the EU (16, 17), Savyon Diagnostics recommends the following interpretation of results:

IgA IU/ml	Result
<12 IU/ml	**Negative**
>12 IU/ml	**Positive**

IgG/IgA antibody profiling: In order to achieve a comprehensive antibodies profile, Savyon Diagnostics recommends testing IgA levels:

IgG	IgA	Interpretation
Negative	Negative	*No indication of B. pertussis infection (see test limitations)*
Intermediate	Negative	*No recent infection*

Intermediate or Negative	Positive	*Indication of recent infection*
Positive	Negative or Positive	*Indication of recent infection*

See **Appendices** for further details in the provider package inserts.

6.3. Quality control and monitoring procedures

The use of control samples in laboratory studies is aimed at identifying unacceptable random and systematic errors at the analytical stage of the study. The result of the measurement of the control sample is used to estimate the measurement error of the laboratory indicator in the studied samples. The principle of conducting laboratory quality control for enzyme immunoassay: each time the test is run, 3 measurements of the same control material are taken with the patient's serum samples, and the results of these measurements are entered into the Shewhart control card. As a control sample, an interlaboratory standard is used, which (unlike international or national standards) can be prepared in the laboratory independently.

7. Statistical analysis

This is a cross-sectional sero-survey study in a population sample aged ≥ 10 and < 19 years of age. The data will be analysed descriptively. The database will contain several sections with different variables: for demographic, socio-economic, vaccination status, and infection risk factors. The questionnaires will be grouped by grade and section to facilitate data entry. Information from the questionnaires will be entered into an online form created using Google Forms by specialists in 4 regions. Input inconsistencies found will be corrected by rechecking the relevant questionnaires until a clean database will be received. The data will be validated according to a logical sequence of questions. For this purpose, prime frequencies will be calculated for all variables, allowing inconsistencies and incomplete information to be detected. Any discrepancies found will be discussed by the principal investigators to determine the action to be taken, and changes will be made by a single data scientist. This completes the data cleansing process.

EpiInfo 7 software for Windows will be used to calculate simple averages and frequencies, taking into account a confidence interval (CI) of 95% and to determine the statistical significance of the results obtained ($p < 0.05$). Descriptive statistical tests, proportions and mean will be used to calculate demographic and socioeconomic factors, immune status and risk of infection.

The analysis will be conducted using the Statistical Package for the Social Sciences (SPSS). Correlations between age group and anti-RT antibody levels will be analysed using multivariate regression or regression splines. Binary and multivariate logistic regression analysis will be used to determine the relationship and influence of independent variables on the dependent variable.

8. Administrative and regulatory requirements

8.1. Administrative data handling

Study documents and retention of records

Study documentation includes all investigation forms, workbooks, laboratory reports, data correction forms, source documents, monitoring logs, sponsor/investigators correspondence, Ethics Committee/regulatory documents (e.g., confidentiality agreement, signed protocol and amendments, inventory list, shipping letter, etc.), and any other reports or records of procedures performed in accordance with the protocol. Whenever possible, the original recording of an observation should be retained as the source document.

All study documents will be archived for five (5) years by the Principal Investigator at the study center. A copy of all CRFs will be archived for five (5) years after the results of the study have been published in a peer-reviewed journal.

Data Quality Assessment

The investigation form should be provided to all participants to collect demographics and risk factors data. Upon consent, all information requested in the investigation form should be completed. The Investigators will be responsible for implementing and maintaining quality control and quality assurance systems to ensure that the data are recorded in compliance with the protocol, standards of good scientific conduct, and all applicable government and local laws.

8.2. Ethics and regulatory

This is a cross-sectional observational study with no intervention. Thus, the study is not relevant for safety assessments of medicines. Information on medicinal products (post-authorization studies) or safety reporting will not be performed. However, routine pharmacovigilance will be collected as per the regulation in place.

As described in the study procedures, written informed consent will be sought from the participants or the parents or legal guardians before any samples or data will be obtained. Data on demographics' characteristics including household characteristics and vaccination history will be collected using an IF. To obtain approval to conduct this study the protocol will be submitted for approval to the Local Ethical Committee.

The study will meet the following ethical criteria:

Patient risk: Patients will be subject to minimal risk. Blood draws will be performed only by Kazakhstani trained personnel.

Autonomy: Informed consent and assent will be obtained before study enrollment.

Benefit: The study provides a public health benefit, as it will provide data that will inform the decision of whether Kazakhstani authorities should implement routine booster immunization.

Justice: All participants meeting study criteria will be invited to enroll regardless of race, ethnicity, gender, socioeconomic status, or other characteristics.

Compliance to Law

The Investigators agree to conduct the study in an efficient and diligent manner in accordance with this protocol and local laws, rules, and regulations including the latest version of the declaration of Helsinki (Appendix B), the guidelines of Good Epidemiology Practices (Appendix C), and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) regulatory guidelines. The applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research will be followed.

The Investigators shall prepare and maintain complete and accurate study documents. Study documents will be promptly and fully disclosed by the Investigators upon request and will be made available at the Investigators' site upon request for inspection, review, and audit by any regulatory agency representatives.

Data Protection

For data protection purposes, individuals involved in the study processes must ensure the confidentiality of the data of the study participants. Furthermore, all must assure compliance with the law on Personal Data Protection in Kazakhstan and any further regulations governing the security measures that shall be adopted to keep the data confidential. Study subjects will be identified by a unique study number and the use of personal names, addresses, phone numbers or any other data that directly identifies the participant or his/her family will be avoided. Date of birth will be used to confirm the participant’s current age. The sponsor will comply with the existing law regarding data protection in Kazakhstan.

9. Communication and publication

In the interest of scientific openness and in order to inform the wider medical and scientific community, the investigator of the study team are jointly committed to submit for publication to a (inter)national conference or a reputable peer-reviewed journal an abstract/manuscript relating to the Study within a period of six (6) months following the finalization of the Statistical Analyses. Any publication draft in whatever form (manuscript, abstract, or presentation) will be circulated to all investigators of the study team for review and to comment on the contemplated publication draft.

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Appendices

Appendix 1. Study questionnaire and data log

Case report form - 06May19aa.xlsx

Appendix 2. Informed Consent Forms

Written Informed consent must be given to all enrolled participants or to their parent/guardian

INFORMED CONSENT FORM Iraq

Appendix 3. Declaration of Helsinki

Adobe Acrobat 7.0 Document

Appendix 4. Good Epidemiological Practices

Adobe Acrobat 7.0 Document

Appendix 5. Savyon Diagnostics Ltd - SeroPetussis® Package Insert

SeroPertussis_Toxin_IgA_1233-01E.V09-(

SeroPertussis_toxin_IgG_1231-01E.V08-