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Burden of major cancer types in Almaty, Kazakhstan

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Globally, cancer is the second leading cause of death, with a growing burden also observed in Kazakhstan. This study evaluates the burden of common cancers in Almaty, Kazakhstan's major city, from 2017 to 2021, utilizing data from the Information System of the Ministry of Health. In Kazakhstan, most common cancers among men include lung, stomach, and prostate cancer, while breast, cervical, and colorectal cancers are predominant among women. Employing measures like disability-adjusted life years (DALYs), we found that selected cancer types accounted for a total DALY burden of 25,016.60 in 2021, with mortality contributing more than disability (95.2% vs. 4.7%) with the ratio of non-fatal to fatal outcomes being 1.4 times higher in women than in men. The share of non-fatal burden (YLD) proportion within DALYs increased for almost all selected cancer types, except stomach and cervical cancer over the observed period in Almaty. Despite the overall increase in cancer burden observed during the time period, a downward trend in specific cancers suggests the efficacy of implemented cancer control strategies. Comparison with global trends highlights the significance of targeted interventions. This analysis underscores the need for continuous comprehensive cancer control strategies in Almaty and Kazakhstan, including vaccination against human papillomavirus, stomach cancer screening programs, and increased cancer awareness initiatives.

The disability-adjusted life year (DALY) was introduced by the World Bank in 1993 to assess the worldwide burden of disease and help in prioritizing the development of health policies[1]. The DALY is a quantitative measure that combines both death (measured in years of life lost owing to premature mortality [YLL]) and disability (measured in years lived with disability [YLD]) over a specific period of time. Thus, the main aim of the burden of disease concept is to make disease and death comparable on a unified scale, which is the YLL, allowing for ranking of the impacts of different diseases on population health. To this end, adjustments are made when calculating YLD using disability weights (DW) to weight disease in populations according to level of severity.

Cancer has become the second most common cause of death worldwide[2], estimated at over 18.1 million new cases (without non-melanoma skin cancer) and nearly 10.0 million cancer-related deaths in 2020[3]. This makes cancer the main obstacle to increasing life expectancy in all countries worldwide[4]. The burden of malignant diseases continues to increase globally. A 47% rise in cancer incidence is projected on a global scale by 2040, with most of this increase in transitioning countries owing to population growth and aging[3]. The most prevalent types of malignant neoplasm are breast, lung, colorectal, prostate, stomach, and cervical cancers[5]. Kazakhstan belongs to the countries with a high-middle Socio-Demographic index (SDI) (0.723 in 2019) and is in the early stages of demographic aging with an increasing proportion of older people in the age structure of the country's population (7.1% in 2009 and 8.3% in 2023) and city residents (56.1% in 2009 and up to 61.2% in 2023)[6,7]. Kazakhstan is a country with a relatively young population with high under age 25 fertility rate of 0.867 (over 60% higher than in average in high-middle SDI group of countries, which in year 2019 was 0.537)[8]. At the same time, the socio-economic and cultural landscape of Kazakhstan is characterized by significant differences between urban

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and rural areas and by a multi-ethnic population, both being related with varying health outcomes and unequal access to health services.

Quantifying the burden of cancer is an important tool for cancer control policies, resource allocation, and health system planning[9,10]. The high share of YLL in the burden of most cancer types points to the need for prioritizing resources toward prevention, early detection, and health care to increase survival in patients with cancer. However, an increasing share of YLD indicates improved early detection and better survival. This would bring the focus of health care to improve quality of life among patients with cancer, to avoid progression and to achieve cure in some cases.

One example of the escalating impact of the cancer burden involves malignancies of the respiratory tract[11]. According to the Global Burden of Disease (GBD) study, tracheal, bronchus, and lung cancer (i.e., lung cancer) rank among the 20 leading causes of DALYs globally, rising from the 20th position in 2000 (32,285,637.30 DALYs) to the 14th position in 2019 (45,857,963.50 DALYs)[10]. However, there has been a similar rise in the DALYs for nearly all types of cancer globally, excluding stomach cancer, liver cancer secondary to hepatitis B, Hodgkin lymphoma, and leukemia, demonstrating an increasing burden of cancer in both developed and developing countries. In Kazakhstan, the DALYs for lung cancer ranked 13th (99,097.82) in 2000 and shifted to 9th (118,130.34) place in 2019. After lung cancer, the most notable rise in DALYs is observed in colorectal, breast, and pancreatic cancers[11].

In 2019, according to the GBD study, all diseases and injuries in Kazakhstan amounted to 5.8 million DALYs, of which approximately 600,000 were associated with malignant neoplasms. Compared with countries in the Central Asia region (9.5%), the proportion of DALYs associated with cancer in Kazakhstan (10,4%) is slightly higher than that in Uzbekistan (7.7%), Kyrgyzstan (7.6%), and Tajikistan (6.7%) and is lower than that in other neighboring countries (Azerbaijan 11.5%, Armenia 15.8%, Mongolia 14.6%)[12].

During 2021 in Kazakhstan, of 32,572 registered new cases of cancer, the most common types were breast (15.4%), lung (11.1%), stomach (7.9%), cervical (5.5%), lymphatic and hematopoietic (5.3%), colon (5.2%), and rectal (4.9%) cancers. Cancer of the lung, stomach, and prostate were the leading pathologies in the male population whereas breast, cervical and colorectal cancer predominated among women. According to the oncological registry of the Republic of Kazakhstan, in 2021 the city of Almaty exhibited a lower incidence and mortality rates for lung, stomach, rectal, and cervical cancers compared with the national averages across Kazakhstan. Conversely, analogous indicators for breast cancer, colorectal cancer, and prostate cancer surpassed the nationwide averages[13].

To our knowledge, no studies have been conducted to assess DALYs attributed to cancer on a regional level in Kazakhstan. Therefore, the objective of our study was to assess the prevalence, mortality, and DALYs associated with the most frequent types of cancer based on the best available national data sources in the largest city of Kazakhstan, namely, Almaty. The results were compared with existing estimates for other capitals or large cities in high-, middle-, and low-income countries to better assess the cancer epidemiology in Kazakhstan.

Methods

This study was conducted in Almaty, the most populous city in Kazakhstan, which had approximately 2 million inhabitants as of 2021. The study was roughly based on the GBD study methodology[11]. This study was carried out as part of the project CATINCA (Capacities and Infrastructures for Health Policy Development). The burden associated with the most prevalent cancer types in both sexes was determined using data from annual reports of the oncological service of the Republic of Kazakhstan from 2017 to 2021[13]. The burden of cancer was assessed using the DALY indicator, which is the sum of YLD and YLL[14]. This indicator reflects the loss of life years owing to non-fatal and fatal consequences of disease[15].

Types of cancer

This study included six types of cancer with the corresponding International Classification of Disease Tenth Revision codes, corresponding to the GBD study: cancer of the trachea, bronchus, and lung (i.e., lung cancer, C33–C34.9), colorectal cancer (C18–C21.9), stomach cancer (C16–C16.9), breast cancer (C50–C50.9), cervical cancer (C53–C53.9), and prostate cancer (C61–C61.9). In 2017, the most common cancer types by incidence in Kazakhstan for both sexes were breast, lung, colorectal, stomach, cervical, and prostate cancers[13]. These cancers (except stomach cancer) are also among the most common cancers in Europe. Colon cancer and rectal cancer are recorded separately in the oncological register of Kazakhstan and were combined into one group for the calculations. At the same time, rectal cancer and anal cancer were combined (C19–C21) and included in the colorectal cancer group. Breast cancer in men is generally rare; therefore, only women were included in the calculations. Isolated cases of cervical cancer in men were also recorded in the data and assigned to women.

Population data and standardization

Population data for Almaty were taken from public sources, namely, the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan and the Bureau of National Statistics website, based on the national population census, the most recent of which took place in 2009 and 2021[16]. The population of Almaty ranged from 1,553,267 in 2017 to 1,977,258 people in 2021, making up between 8.5 and 10.5% of the total population of Kazakhstan. The direct method of standardization was applied using the GBD 2019 World Standard Population[17].

Mortality data and YLL calculation

Data from the Information System of the Ministry of Health (ISMH) of the Republic of Kazakhstan on the incidence and mortality for selected types of cancer were provided upon request by the Republican Center for Electronic Health (RCEZ) of the Ministry of Health, where data are collected on numerous public health indicators,

including the oncological registry of Almaty. Upon request, aggregated cancer mortality data were provided, broken down by disease code, age group, sex, and year of death in the city of Almaty. There were 18 age groups in total, in 5-year intervals from age 0 to 85 years and older. Because mortality data were only provided from 2017 onward, all calculations were for the period from 2017 to 2021. Mortality data provided by the RCEZ were reconciled with annual reports from the oncological service of the Republic of Kazakhstan. The match between the two sources was 98–99% over the different years.

Using YLL, the disease-specific impact of mortality on population health is measured, considering the age of deceased individuals. Thus, the YLL reflects the burden of disease in terms of the statistically identified number of potential years of life not lived, and therefore, the number of life years lost owing to mortality. In the present YLL calculation, the GBD 2017 standard life expectancy table was used, which was derived from the minimum observed mortality risk within each 5-year age category across national populations worldwide exceeding 5 million inhabitants (the so-called aspirational life expectancy). The GBD tables provide one uniform life expectancy for both sexes[18]. Life expectancy corresponding to the midpoint of the 5-year age range was used to calculate age-specific YLL. YLL for all cancers for each sex and by age were calculated using the formula:

$$YLL = \sum_{i=1}^{n} D_I \times RLE_i$$

where I is the age group, D is the number of deaths, and RLE is residual life expectancy.

GBD standard life expectancies allow for comparisons of YLL between countries. However, the actual life expectancy in the Republic of Kazakhstan, and thus, the realistic number of YLL, are considerably lower. Comparisons of GBD life table life expectancy estimations by the World Health Organization (WHO), based on national Kazakh vital statistics, can be seen in Supplementary Fig. 1.

In line with the current GBD methodology and the WHO, we did not discount future unlived years and we did not weight according to age[19].

Prevalence data and YLD calculation

As in the GBD study we used 10-year-prevalence as the basis to calculate YLD. However, we used Kazakh registry data in order to directly estimate the 10-year prevalence[20]. Prevalence data for this study were also obtained from the ISMH at individual level in the form of a list of patients diagnosed with cancer, with the date of birth, disease code, date of diagnosis, and date of death when applicable. The 10-year-prevalence was calculated for the reference years 2017–2021. This meant that patients diagnosed within 10 years before one of these reference years and who were still alive in the reference year were considered prevalent cases and categorized by age group, sex, and cancer type. Cancer prevalence also included patients in terminal stages who died from the disease within the reference year. For these cases, it was assumed that death occurred in the middle of the year, thereby incorporating 6 months into the YLD estimations. The received data did not contain information about treatment and therefore did not allow for estimation of the frequencies of different severity grades in the diseased population. According to the GBD methodology, many cancers exhibit at least four categories of sequelae: diagnosis and primary therapy; controlled; metastatic; and terminal phases with specific variations for the controlled phase such as colostomy for colorectal cancer, mastectomy for breast cancer, infertility for cervical and prostate cancer; and others[20]. For this study, the prevalence of each cancer sequela in Kazakhstan was sourced from the GBD 2017 study, stratified by sex and age[21]. To check the sensitivity of GBD sequelae in the final results for some types of cancer (except cervical cancer and stomach cancer), we used age- and sex-specific severity distributions from the German Burden of Disease Study[22,23]. The respective distribution of sequelae was applied to the population with disease from national Kazakh data. YLD for each sequela were calculated using the following formula:

$$YLD = \sum_{i=1}^{n} P_{Sxi} \times DW_{Sxi}$$

where i is the age group, x is the cancer sequela, P_S is the 10-year prevalence of cancer sequela, and DW_S is the disability weight (DW) for cancer sequela.

DWs for each health state were derived from the GBD 2013 study, which were calculated using various methods, including expert and general population surveys (Supplementary Table S1)[24]. The sum of YLD for all sequelae represents the final estimate of YLD associated with each type of cancer.

To conduct a comparative analysis of DALY rates for specific cancer types in Almaty, we examined analogous metrics from major cities in Germany and Scotland, as well as from Mexico and Indonesia. This analysis also encompassed comprehensive data for the entirety of Kazakhstan and the broader Central Asian region, to which Kazakhstan is integral. We decided to make a comparison between different major cities of the world. Our sample included Glasgow and Berlin, for which data are readily available in public national databases. We also randomly selected the cities of Mexico City and Jakarta, with similar SDIs to Kazakhstan (0.732 and 0.802, respectively) for which we extracted data from the GBD 2019 study results tool. Data for Berlin were also available from the German Burden of Disease study, for which we had data with age distribution. YLL data from the German Burden of Disease Study (BURDEN 2020) on Berlin, the largest German city, were recalculated for the present study using the GBD study life expectancy estimates.

Results

Morbidity and mortality

In 2021, the city of Almaty reported a total of 2018 newly diagnosed cases and 921 recorded deaths attributed to stomach, lung, colorectal, breast, prostate, and cervical cancers. The most prevalent cancers observed were prostate and colorectal cancers in men and breast and cervical cancers in women. The highest mortality rates were associated with lung and stomach cancer in men and breast and colorectal cancer in women (Table 1).

When comparing indicators in 2017 and 2021, a decrease in the crude and age-standardized rates of prevalence and mortality was observed for nearly all types of cancer. Exceptions were noted for stomach cancer in men, where both crude and standardized mortality rates showed an increase by 5.5% and 2.6%, respectively. Additionally, for colorectal cancer in men, an increase in crude 10-year prevalence rates (by 5.0%) was observed, accompanied by a decrease in standardized rates by − 2.0%. The most notable difference between 2017 and 2021 was found in women, revealing a substantial rise in both the crude and standardized 10-year prevalence rates for lung cancer, by 15.9% and 0.41%, respectively.

Absolute numbers and age-standardized rates for DALY

Absolute DALYs

Cancers of specified types accounted for a total of 25,016.70 DALYs in Almaty during 2021, with a distribution of 95.2% attributed to YLL and 4.7% to YLD. Among these, the most substantial burden was linked to lung and stomach cancers in men and to breast and colorectal cancers in women (Fig. 1). The total DALYs attributed to the selected cancer types in 2021 amounted to 14,270.90 DALYs in women and 10,745.80 DALYs in men.

Relative changes in DALYs between 2017 and 2021

The burden associated with the selected cancers rose from 22,105.70 DALYs in 2017 to 25,016.60 in 2021, representing a 13.2% relative increase (Table 2). Among the selected cancer types, the most noticeable rise in absolute DALYs was observed for stomach cancer in in men (+ 30.7%) and women (+ 40.2%). This observed rise was primarily attributable to population growth. In contrast, age-standardized DALYs for these cancer types declined in total from 2,015.80 to 1,609.80 per 100,000 individuals, a notable reduction of 16.0% primarily attributed to YLL.

Over the course of 4 years, the age-standardized DALY rate per 100,000 increased only for stomach cancer in men; for all other cancer types, a decrease in the rate was noted in both men and women (Fig. 2). The most substantial reduction was found in prostate cancer among men, and lung and breast cancer among women. Notably, this decline was more closely associated with a decrease in YLL (− 36.0% for prostate cancer and − 40.6% for lung cancer in women) than in YLD (Supplementary Table S2).

Ranking

In 2017, the most substantial burdens affecting both sexes were for lung cancer, followed by breast, colorectal, stomach, cervical, and prostate cancer. In 2021, breast cancer was in the leading position, followed by lung, stomach, colorectal, cervical, and prostate cancer. Figure 3 presents a comparative ranking of selected cancers in Almaty by age-standardized DALY rates per 100,000 population, for both men and women, spanning from 2017 to 2021. The lung cancer rank decreased by one position whereas breast cancer ascended by a single position within the observed period. All other cancer types maintained their respective standings, with prostate cancer exhibiting the most pronounced reduction in DALY rates.

Cancer type	Prevalence, crude (age-standardized*)		Mortality, crude (age-standardized*)	
	2017	2021	2017	2021
Men				
Lung	38.4 (49.1)	39.4 (45.0)	19.0 (23.8)	17.5 (20.8)
Breast	–	–	–	–
Colorectal	74.6 (96.8)	78.3 (94.9)	9.6 (12.3)	8.8 (11.8)
Stomach	33.7 (43.2)	32.2 (38.4)	10.9 (13.7)	11.47 (14.1)
Cervical	–	–	–	–
Prostate	125.6 (177.6)	115.1 (161.6)	9.87 (14.7)	6.7 (10.2)
Women				
Lung	24.7 (24.1)	28.6 (24.2)	7.84 (7.6)	5.3 (4.7)
Breast	538.5 (501.2)	456.7 (387.1)	22.18 (20.4)	17.1 (14.4)
Colorectal	107.6 (103.1)	94.8 (79.3)	10.76 (9.7)	9.7 (8.4)
Stomach	27.1 (25.4)	23.1 (19.1)	6.51 (5.7)	5.6 (4.8)
Cervical	196.5 (176.6)	147.8 (127.6)	6.91 (6.3)	5.6 (4.8)
Prostate			–	–

Table 1. Crude and age-standardized prevalence and mortality rates for certain cancer types per 100,000 in Almaty in 2017 and 2021. *Standardized using the Global Burden of Disease 2019 Standard World population.
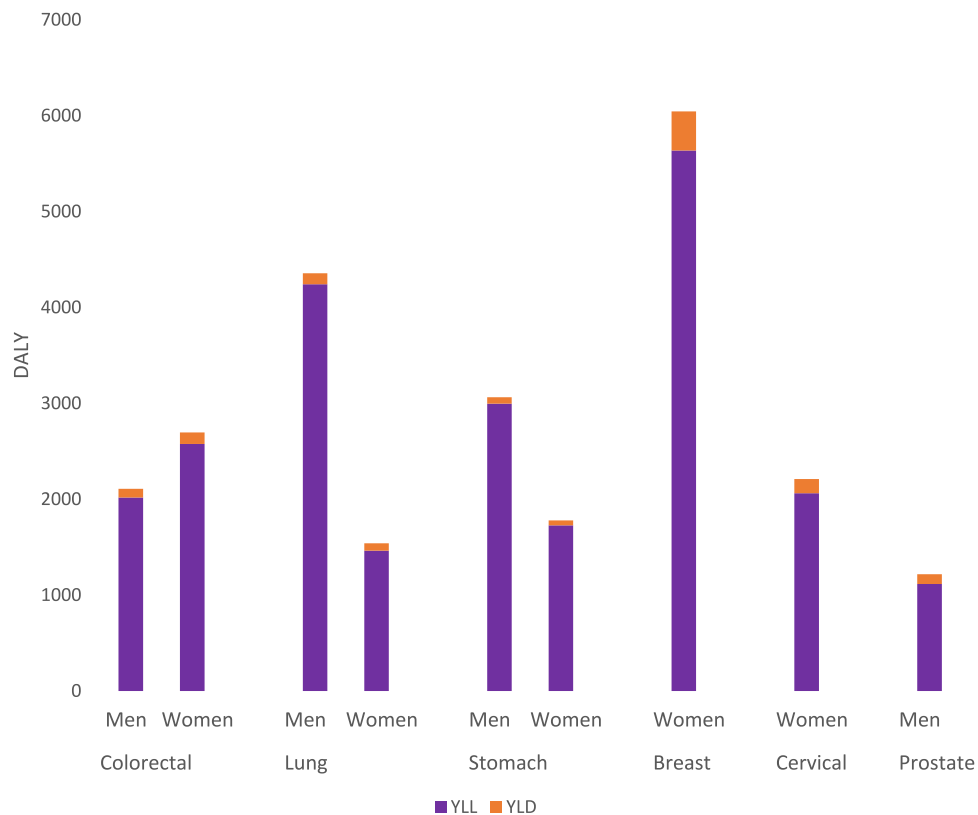
Fig. 1. Disability-adjusted life years (DALYs) according to sex for each selected cancer type with proportions of years lived with disability (YLD) and years of life lost owing to premature death (YLL) in Almaty, 2021. Disability-adjusted life years (DALYs), delineated in this figure for Almaty in 2021, encompass both the years lived with disability (YLD, represented in orange) and the years of life lost to premature mortality (YLL, depicted in purple), with these metrics disaggregated by sex for selected cancer types.

The largest cancer burden among men exhibited no change in 2017 and 2021 and was primarily attributed to lung cancer, followed by stomach, colorectal, and prostate cancer.

The foremost contributors to DALYs among women remained consistent in both 2017 and 2021. These were breast cancer, followed by colorectal cancer and cervical cancer. In 2017, the fourth and fifth positions among the selected cancer types were for lung and stomach cancer, respectively. In 2021, there was a reversal in these rankings, with stomach cancer surpassing lung cancer among women in Almaty. The primary cancer burden among women in both 2017 and 2021 was owing to breast cancer, followed by colorectal, cervical, lung, and stomach cancers. Notably, in 2021, the absolute DALYs for stomach cancer exceeded those of lung cancer in women (Supplementary Figs. S1 and S2).

YLD and YLL proportions

The proportion of YLD in the total DALYs differed depending on the type of cancer, with minimal values observed for stomach cancer (2.4%) and lung cancer (3.3%) and maximum proportions noted for breast cancer (6.7%) and prostate cancer (8.4%) in 2021. In women, the proportion of total YLD (for all observed cancers) constituted 5.6% whereas in men, YLD for the selected types of cancer accounted for 3.4%, with the difference in the ratio of non-fatal to fatal consequences (YLD:YLL) being 1.4 times higher in women. In the case of neoplasms affecting both sexes, including lung, colorectal, and stomach cancers, the ratio of YLD:DALYs was also 1.4 times higher than in men. Between 2017 and 2021, a relative reduction in the YLL proportion was apparent for prostate cancer (− 2.9%), breast cancer (− 0.8%), lung cancer (− 0.7%), and colorectal cancer (− 0.3%). Conversely, there was a slight relative increase in the YLL proportion for cervical and stomach cancer (+ 0.2% and + 0.2%, respectively) (Fig. 4).

Age distribution of DALY by cancer type

DALYs per 100,000 people for the selected cancer types in both sexes remained relatively low until age 35 years, beyond which a gradual increase was observed (Fig. 4). Among men, the highest rates were identified in the age group 65–74 years for lung and stomach cancer and 75–84 years for colorectal cancer and prostate cancer. For women, the age ranges at which the highest DALY rates per 100,000 were observed were for breast cancer, with a first peak occurring at age 45–54 years and a second peak at age 65–74 years.

Cancer type	DALY, years			DALY rate per 100,000, Crude (age-standardized)			YLL proportion of DALY, %		
	2017	2021	Relative change (%)	2017	2021	Relative change (%)	2017	2021	Relative change (%)
Both sexes*									
Breast	5352.7	6045.2	12.9	344.6 (333.0)	305.7 (286.6)	− 20.6 (− 23.4)	94.0	93.3	− 0.8
Lung	5667.8	5901.8	4.1	364.9 (374.2)	298.5 (285.3)	− 18.2 (− 23.7)	97.4	96.7	− 0.7
Colorectal	4013.8	4805.7	19.7	258.4 (264.6)	243.0 (239.1)	− 5.9 (− 9.6)	96.0	95.6	− 0.3
Stomach	3612.6	4842.7	34.1	232.6 (234.0)	244.9 (232.9)	5.3 (− 0.5)	97.3	97.6	0.2
Cervical	1874.3	2210.6	17.9	120.7 (105.5)	111.8 (95.1)	− 17.0 (− 20.5)	93.1	93.3	0.2
Prostate	1584.5	1217.5	− 23.2	102.0 (113.0)	61.6 (63.9)	− 32.2 (− 34.0)	94.3	91.6	− 2.9
Total	22,105.7	25,016.6	13.2	2013.8 (2015.8)	1692.1 (1609.8)	− 16.0 (− 20.1)	95.7	95.3	− 0.5
Men***									
Lung	4011.7	4356.1	8.6	501.2 (579.9)	480.3 (543.2)	− 4.2 (− 6.3)	97.6	97.4	− 0.2
Stomach	2343.5	3063.5	30.7	292.8 (334.7)	337.7 (376.3)	15.4 (12.4)	97.6	97.8	0.2
Colorectal	2010.0	2108.6	4.9	251.1 (290.3)	232.5 (278.7)	− 7.4 (− 4.0)	96.4	95.7	− 0.7
Prostate	1584.5	1217.5	− 23.2	198.0 (281.5)	134.2 (185.9)	− 32.2 (− 34.0)	94.3	91.6	− 2.9
Total	9949.7	10,745.8	8.0	1243.1 (1486.4)	1184.7 (1384.2)	− 4.7 (− 6.9)	96.8	96.5	− 0.3
Women***									
Breast	5352.7	6045.2	12.9	711.0 (638.9)	564.9 (489.5)	− 20.6 (− 3.4)	94.0	93.3	− 0.8
Colorectal	2003.2	2696.1	34.6	266.1 (248.5)	251.9 (220.0)	− 5.3 (− 11.5)	95.5	95.6	0.1
Cervical	1874.3	2210.6	17.9	249.0 (222.6)	206.6 (177.1)	− 17.0 (− 20.5)	93.1	93.3	0.2
Lung	1653.5	1540.1	− 6.9	219.6 (211.7)	143.9 (125.8)	− 34.5 (− 40.6)	97.1	95.0	− 2.2
Stomach	1268.9	1778.9	40.2	168.5 (151.1)	166.2 (142.2)	− 1.4 (− 5.8)	96.9	97.1	0.3
Total	12,152.7	14,270.9	17.4	1614.2 (1472.8)	1333.5 (1154.6)	− 17.4 (− 21.6)	94.8	94.4	− 0.5

Table 2. Absolute numbers and rates per 100,000 population of DALY and YLL proportion for selected cancer types with relative changes in 2017 and 2021 in Almaty* *Standardized using the Global Burden of Disease 2017 Standard World population. **Rates for all cancer types were computed for both men and women. ***Rates for cancer types were computed for the respective sexes. *YLL* years of life lost, *DALY* disability-adjusted life year.

Cervical cancer displayed a peak in the DALY rates in the age group 45–54 years, with a slight decline observed in the age group 65–74 years. Both stomach and lung cancer demonstrated their highest DALY rates in the age group 65–74 years. However, colorectal cancer rates began to ascend notably from the age group 55–64 years, reaching their peak in the age group 75–84 years (see Fig. 5).

Sensitivity analysis: YLD for Almaty based on German severity distribution

Owing to the absence of Kazakh data on the frequency of sequelae, two sources were used for the DALY calculations, estimations from the GBD study for Kazakhstan and data from the German Burden of Disease study[22,25]. In the German study, data were available for breast, colorectal, lung, and prostate cancers. Upon applying the German severity distribution to the 2021 Almaty data, breast cancer resulted in 647.0 YLD, marking a 37% increase compared with the 407.9 YLD calculated using Kazakhstan's severity distribution from the GBD study. A comparable trend was evident in the cases of prostate cancer (+ 25.8%), colorectal cancer in men (+ 18.3%), and colorectal cancer in women (+ 14.2%). Conversely, when applying the German severity distribution data to calculate the YLD for lung cancer in men, the figures were lower than those calculated using the GBD study's severity distribution data, with a difference of − 21.1%; for lung cancer in women, a difference of − 4.2% was observed. In the distribution of different stages of breast cancer within the German and GBD studies, a disparity was observed in the controlled phase, with and without mastectomy. Within the German data, the proportion of these two stages was relatively balanced within the disease structure, accounting for 47% and 39%, respectively.
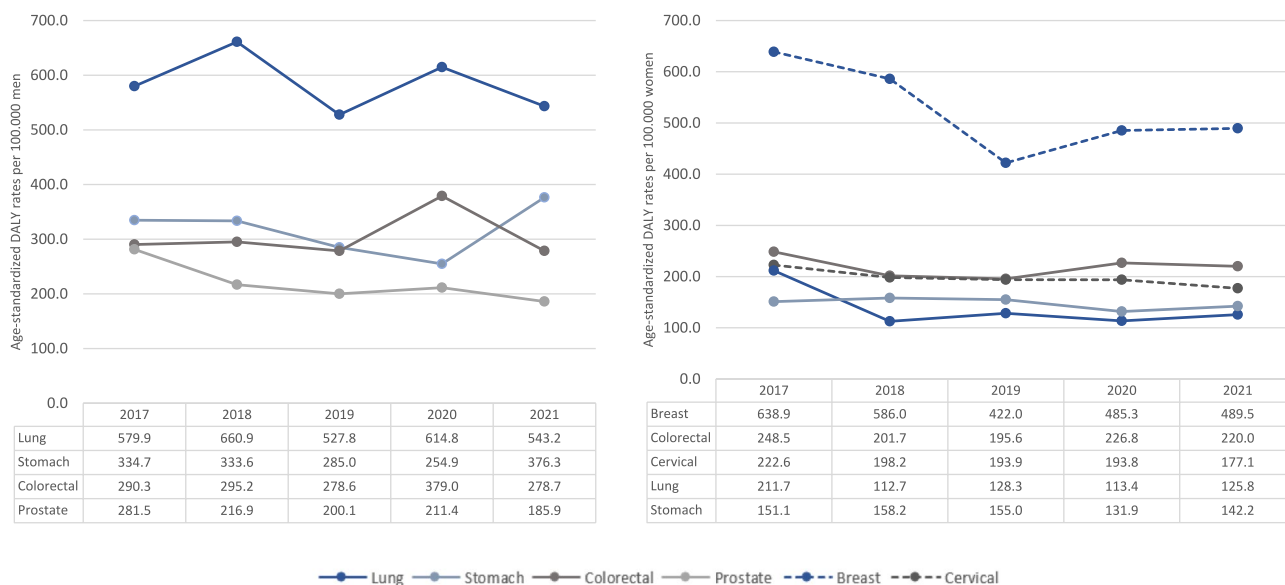
Fig. 2. Age-standardized disability-adjusted life years (DALYs) rates for certain types of cancer in men (left) and women (right) from 2017 to 2021 in Almaty. This figure shows trends in age-standardized disability-adjusted life years (DALYs) rates per 100.000 population among men and women in Almaty over the 5-year period, 2017 to 2021, for lung, stomach, colorectal, prostate, breast, and cervical cancers.
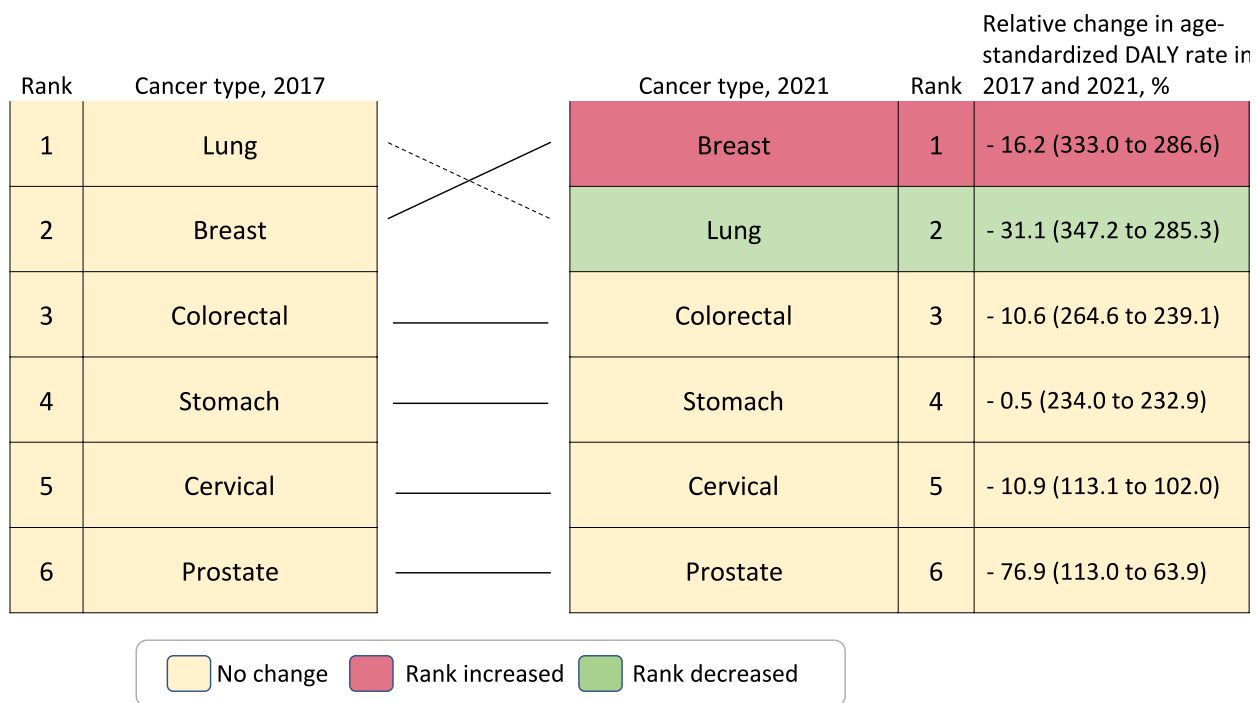
Rank	Cancer type, 2017		Cancer type, 2021	Rank	Relative change in age-standardized DALY rate in 2017 and 2021, %
1	Lung		Breast	1	- 16.2 (333.0 to 286.6)
2	Breast		Lung	2	- 31.1 (347.2 to 285.3)
3	Colorectal		Colorectal	3	- 10.6 (264.6 to 239.1)
4	Stomach		Stomach	4	- 0.5 (234.0 to 232.9)
5	Cervical		Cervical	5	- 10.9 (113.1 to 102.0)
6	Prostate		Prostate	6	- 76.9 (113.0 to 63.9)

No change   Rank increased   Rank decreased

Fig. 3. Ranking of selected cancers based on age-standardized disability-adjusted life year (DALY) rates in both sexes between 2017 and 2021. This figure shows comparative rankings of selected cancers based on age-standardized disability-adjusted life year (DALY) rates in Almaty for both sexes, compared with 2017 and 2021. Changes in ratings are indicated by color coding: red indicates an escalation in ranking, green signifies a decline, and yellow means no change. The accompanying percentages and brackets represent the relative change in age-standardized DALYs between two years for each cancer type.

The GBD data for Kazakhstan depicted the controlled phase without mastectomy as predominating over all other stages, constituting 81%, whereas the phase with mastectomy comprised 12%. In the computation of DALYs, the relative discrepancy in total DALYs between the GBD and German severity distribution varied from − 0.5% to + 3.8%, given that the predominant component of the DALY metric is YLL. For more detailed results, refer to Supplementary Table S2.
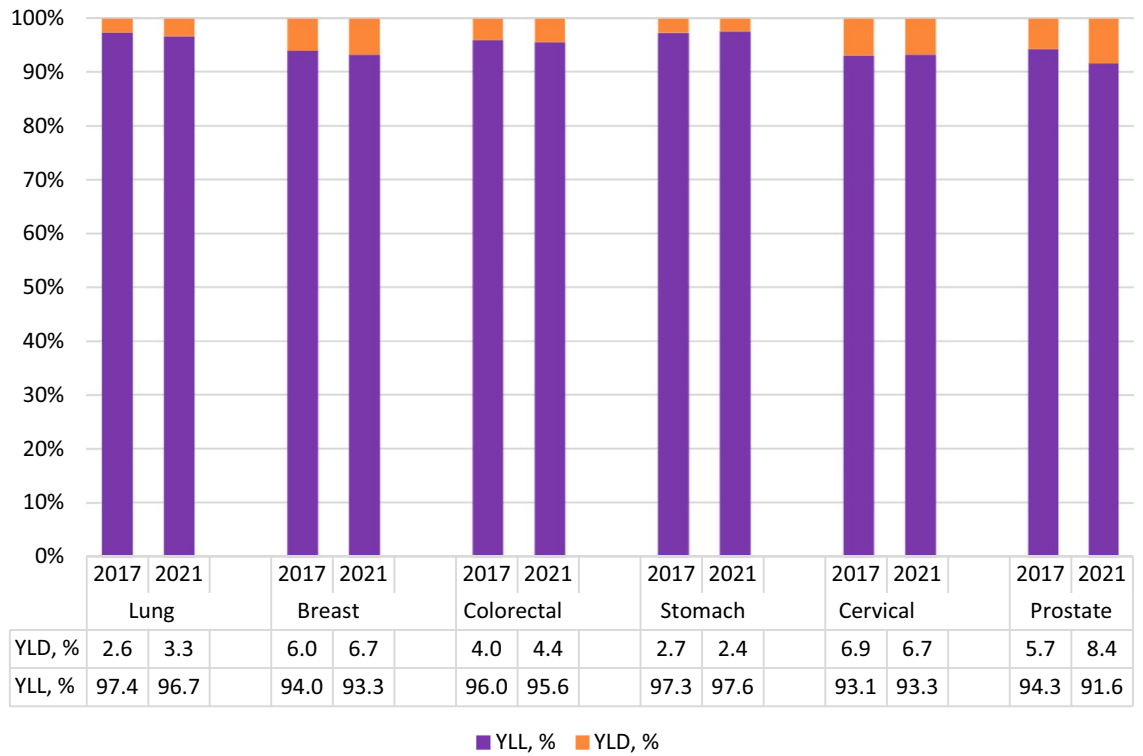
	Lung			Breast			Colorectal			Stomach			Cervical			Prostate	
	2017	2021		2017	2021		2017	2021		2017	2021		2017	2021		2017	2021
YLD, %	2.6	3.3		6.0	6.7		4.0	4.4		2.7	2.4		6.9	6.7		5.7	8.4
YLL, %	97.4	96.7		94.0	93.3		96.0	95.6		97.3	97.6		93.1	93.3		94.3	91.6

Fig. 4. Contribution to disability-adjusted life years (DALYs) of years lived with disability (YLD) and years of life lost owing to premature death (YLL) by cancer type and sex in 2017 and 2021, Almaty. This figure shows the proportional contribution of years lived with disability (YLD, shown in orange) and years of life lost due to premature death (YLL, shown in purple) to total disability-adjusted life years (DALYs) for each specific case by cancer type and sex in Almaty for lung, breast, colorectal, stomach, cervical and prostate cancer, reflecting temporal changes in disease burden over the period 2017–2021.
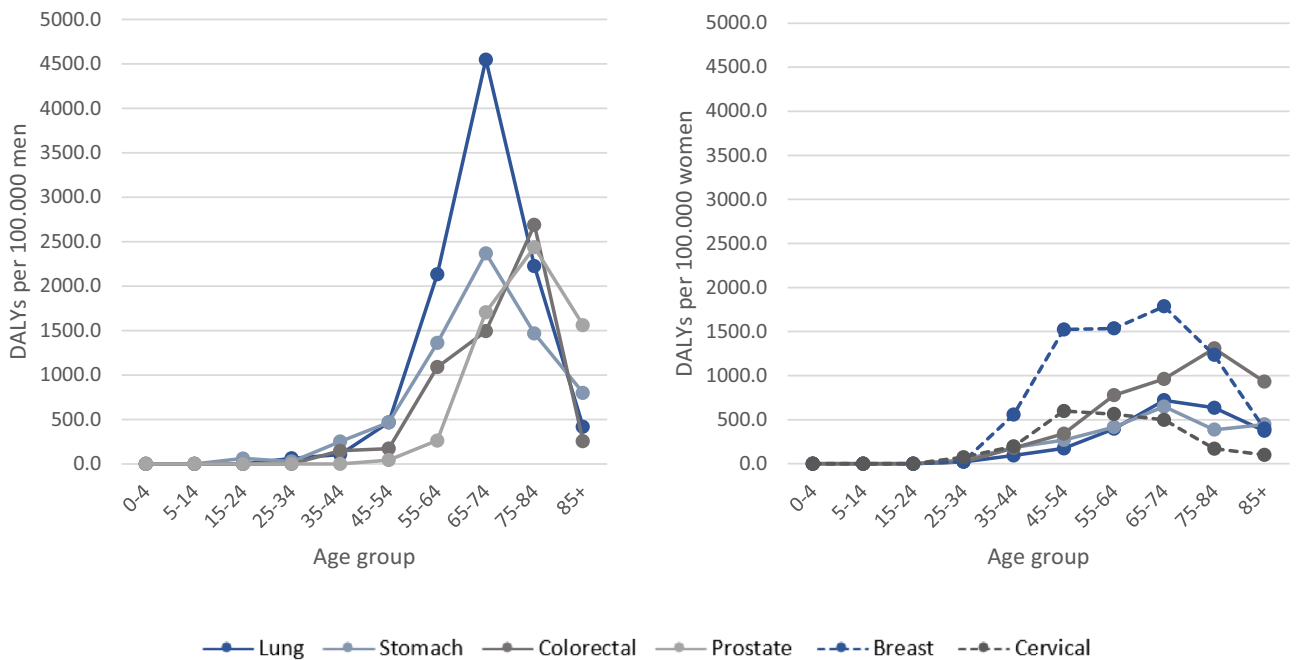
Fig. 5. Age distribution of disability-adjusted life year (DALY) rate per 100,000 in Almaty during 2021 for men (left) and women (right). This figure shows the age distribution of DALYs (disability-adjusted life years) per 100,000 men and women in Almaty in 2021 for age groups from 0–4 years to 85+ years.

Comparative analysis of DALYs in Almaty and other metropolitan areas

We compared DALY rates per 100,000 population in Almaty with similar indicators from studies conducted in major cities of Germany and Scotland, as well as using open data from the GBD study for all of Kazakhstan, Mexico City and Jakarta, as well as Central Asian regions, which include Kazakhstan[25–27]. Overall, the DALY rates based on national data for Almaty were similar to the GBD rates for Jakarta and Mexico City whereas the rates for Glasgow and Berlin derived from national studies tended to be much higher. Almaty generally showed lower DALY rates for colorectal and prostate cancers in men and breast and lung cancers in women, as compared with other locations. Exceptions to the observed trends were discernible in the age-standardized DALY rates for stomach cancer in Almaty, which surpassed those in Glasgow and Jakarta for both sexes and exceeded those for men in Mexico City. Moreover, for the male population of Almaty, DALY rates for lung cancer were elevated in comparison with their counterparts in Mexico City; concurrently, women in Almaty exhibited higher DALY rates for cervical cancer relative to those in Jakarta. Upon comparing DALY rates for Almaty derived from our research with data for Kazakhstan from the GBD study, Almaty presented lower DALY rates for all cancer types across both sexes.

When comparing DALY rates for Almaty in our study and those for all of Kazakhstan from the GBD study, lower rates were observed in Almaty for all cancer types in both sexes. A more detailed presentation of age-standardized DALY rates per 100,000 for the specified regions is provided in Table 3.

To explore age differences between cities, using Berlin and Almaty as examples, the DALY rates attributed to lung, breast, colorectal, and prostate cancers among both men and women were compared for 2020. The burden of these cancer types in Berlin exceeded that of Almaty, particularly in the older age groups. DALY rates for colorectal and prostate cancer in men aged 85+ years were lower in Almaty compared with those in Berlin, by 20 and six times, respectively, with a similar trend in women for colorectal cancer (by four times) and breast cancer (by 10 times). In younger age groups, the differences were minimal or absent in these cities (Supplementary Fig. S2).

Discussion

In this study, we examined the burden of breast, lung, stomach, colorectal, cervical, and prostate cancers in Almaty, Kazakhstan from 2017 to 2021. In 2021, the total burden for selected cancers in Almaty was 25,023.60 DALYs, primarily attributed to death rather than disability. The largest burden was seen in men for lung and stomach cancer; in women, breast and colorectal cancer had the largest burden. Non-fatal burden (YLD) proportion in DALY increased for almost all selected cancer types, except stomach and cervical cancer over the observed period in Almaty. The non-fatal to fatal burden ratio for all selected cancer types was higher in women than in men, meaning that the proportion of total YLD in the total DALYs was 1.6 times higher for women. Men's cancer burden peaked at ages 65–84 years whereas women had two peaks at ages 45–54 years (breast and cervical cancers) and 65–84 years (breast, colorectal, stomach, and lung cancers).

Between 2017 and 2021 in Almaty, the age-standardized prevalence and mortality rates showed a decrease for most cancer types in both men and women. The only exceptions were a 2.6% increase in stomach cancer mortality in men and a slight increase in lung cancer prevalence in women (0.41%). Age-standardized DALY rates exhibited a decline for nearly all cancers in both sexes, averaging 20%, with the exception of stomach cancer in men. The increase in lung cancer prevalence in women is contributing to a rise in YLDs, which accounted for only 5% of DALYs in 2021. Along with a substantial decrease in age-standardized mortality and YLLs, this is leading to a decrease in age-standardized DALY rates. Notably, previous studies reported a decrease in stomach cancer mortality in Almaty from 2009 to 2018. In our study, we noted a gradual decrease from 2017 to 2020, followed by an increase in mortality from 2020 to 2021[28]. This could potentially be related to the COVID-19 pandemic, which may have impacted access to health care, although rates for other cancers did not show an increase. In 2021, Almaty's stomach cancer incidence rates, although slightly higher, were comparable to the global average (ASIR globally in 2020 is 15.8 per 100,000 for men and 7.0 per 100,000 for women). However, stomach cancer

Cancer type	Almaty (2019)	Berlin (2017)	Glasgow (2019)	Kazakhstan (GBD 2019)*	Mexico City (GBD 2019)*	Jakarta (GBD 2019)*	Central Asia region (GBD, 2019)*
Men							
Lung cancer	527.8	1209.4	2567.6	1011.2 (856.3–1179.9)	231.3 (179.4–294.5)	789.3 (477.8–1235.4)	845.2 (750.3–941.0)
Stomach	285.0	n/a	264.7	534.8 (460.1–614.5)	236.8 (185.1–306.2)	145.1 (102.0–195.5)	581.2 8 (524.8–641.7)
Colorectal	278.6	506.5	967.0	378.8 (327.1–439.5)	280.4 (219.5–357.1)	569.4 (292.2–850.4)	305.9 (279.3–337.1)
Prostate	200.1	418.0	328.2	214.2 (168.2–288.0)	326.8 (234.7–445.1)	277.7 (164.5–431.3)	209.8 (167.5–250.3)
Women							
Breast	422.0	712.3	614.9	486.4 (411.2–572.5)	443.7 (349.9–551.8)	623.0 (435.9–880.3)	523.9 (464.1–588.7)
Colorectal	195.6	309.6	775.8	263.6 (226.3–304.0)	206.1 (164.4–256.6)	425.3 (199.5–679.9)	218.8 (198.5–241.4)
Cervical	193.9	n/a	n/a	262.0 (217.6–317.8)	230.8 (175.0–365.8)	172.2 (95.3–284.4)	249.4 (217.4–288.1)
Stomach	155.0	n/a	114.8	214.0 (186.4–246.9)	177.6 (139.7–222.8)	98.0 (58.0–140.5)	261.5 (236.7–290.3)
Lung	128.3	659.9	2294.2	187.7 (156.5–220.9)	145.0 (115.1–180.9)	499.9 (217.0–858.0)	185.2 (165.2–207.5)

Table 3. DALY per 100,000 in Almaty and other cities, countries, and regions among men and women (age-standardized). *DALY* disability-adjusted life year, *GBD* Global Burden of Disease. *Value (lower and upper bounds).

mortality rates for men in Almaty exceeded the global average (14.8 in Almaty vs. 11.0 per 100,000 worldwide). Notably, the highest incidence and mortality rates are in East Asian countries, where the mortality rate for men reaches 21.1 per 100,000 and 8.8 per 100,000 for women[29]. Stomach cancer remains a significant global health concern, ranking fifth in incidence and fourth in mortality worldwide. In Kazakhstan, it ranks second in both morbidity and mortality among men, and fifth and fourth, respectively, among women. The incidence rate is 13.7 per 100,000, and the mortality rate is 9.3 per 100,000 for both sexes, which are higher than the global averages of 9.2 and 6.1, respectively[3]. Given these disparities, it is imperative to implement initiatives to control stomach cancer in Almaty and Kazakhstan in general, including primary prevention through the eradication of *Helicobacter pylori*, especially in people with chronic gastritis or a family history of stomach cancer, as well as the reduction of other risk factors such as excessive salt intake, smoking, obesity, and alcohol consumption[30]. Early detection through the introduction of endoscopic screening is of great importance because it has the potential to reduce mortality by up to 40% in Asian populations[31]. Further research is necessary to investigate the specific risk factors for stomach cancer in Kazakhstan. An increase in lung cancer prevalence in women aligns with the global trend linked to the rise in smoking among women since the 1960s. In Kazakhstan, tobacco consumption in women increased from 4.5% to 10.1% between 2014 and 2021. This rise may be due to the growing popularity of vaping devices, often perceived as safer than traditional tobacco products[32]. The 2021 assessment of DALYs in Almaty showed that breast and lung cancer accounted for the largest burden in both sexes, followed by stomach and colorectal cancer. These data on the cancer burden in Almaty differ from global average trends, where lung cancer typically holds the top position, followed by colorectal and stomach cancer. Notably, the prevalence of these cancers is generally higher in countries with a higher SDI, except for cervical cancer, which is more prevalent in low-SDI countries[11].

The DALY ranks of the selected cancer types in Almaty also differed from those in Kazakhstan as a whole, according to GBD data. In Kazakhstan, cervical cancer overtakes colorectal cancer among women whereas in Almaty colorectal cancer ranks second and cervical cancer ranks third[21]. Comparing the GDB study data obtained for Almaty with data for the whole of Kazakhstan, it can also be noted that the DALY rates for stomach cancer in Almaty did not show the decrease observed in Kazakhstan, which emphasizes that greater attention is needed to the prevention of stomach cancer. For breast cancer, colorectal cancer, and lung cancer in Kazakhstan, based on the GBD study, there is an increase in rank and a decrease in DALYs; in our study, with the same increase in rank, there was a sharper decrease in DALYs, highlighting better survival. In this regard, it is important to note that to assess and discuss the full picture, it is important to also evaluate national data. In Almaty during 2017–2021, men's rankings by absolute DALYs remained stable whereas among women, lung cancer dropped one position and stomach cancer rose one position. Whereas direct comparisons with global rankings are challenging owing to differences in time periods and the limited scope of cancer types in our study, it is informative to note that, globally from 1990 to 2016, the lung cancer DALY rank remained unchanged from the first position. Stomach cancer dropped from second to third place whereas colorectal and breast cancer showed no change; cervical cancer declined by two positions, and prostate cancer ascended one position[20]. The age-specific DALY rates per 100,000 population in Almaty for colorectal, breast, and prostate cancers in the age group 85 years and older were markedly lower compared with those observed in Berlin for the same age category. A similar pattern was observed in a study of DALYs associated with acute myocardial infarction in Kazakhstan in comparison with patients in Portugal, where the highest burden was also found in the older age group[33]. This difference between countries can be explained by variations in health care systems, the mode of detection, patient survival, and access to medical care. Also, sociodemographic and cultural factors, such as the age composition (proportion of the older population) in the two cities had a role, and the care system and social support for older people differ[34]. Data collection and quality may also contribute to the observed differences.

The proportions of YLD and YLL in DALYs in Almaty exhibited similarities to global averages from the GBD study for breast and stomach cancers. The proportion of YLL in Almaty was slightly higher than the proportion of YLL globally for prostate cancer (92% share of YLL in Almaty vs. 91% globally) and colorectal cancer (96% in Almaty vs. 95% globally); this was lower for cervical cancer (93% in Almaty vs. 96% globally) and lung cancer (97% in Almaty vs. 99% globally)[8]. For cancers such as cervical, breast and colorectal cancer, early diagnosis and therapy have a significant impact on disease outcome, potentially increasing YLD at the expense of YLL owing to improved and longer patient survival. Kazakhstan has implemented national screening programs for cervical and breast cancers since 2008 and for colorectal cancer since 2011, potentially explaining the higher YLD rates associated with cervical cancer compared to the global average. In our study, the proportion of the non-fatal burden (YLD) within the total DALY increased for nearly all selected cancer types in Almaty during the observed period, with the exception of stomach and cervical cancers.

The effectiveness of cancer screening programs has been assessed in several studies. From 2009 to 2018, the incidence of breast cancer in Kazakhstan rose from 39.5 per 100,000 to 49.6 ± 0.70 per 100,000 in 2018. However, the proportion of locally advanced and advanced cancer stages decreased, with stage III cases dropping from 22.2 to 8.6% and stage IV cases from 6.4 to 3.6%[35]. Population mammography screening was carried out for women from 50 to 69 years of age, and in 2018 extended for women from 40 to 70 years of age. Up to 30% of breast cancer cases are detected through screening, with 90–95% of these being in the early stages. Breast cancer mortality rates have declined from 16.5 per 100,000 in 2009 to 13.6 per 100,000 in 2020. Although more time is needed to fully assess the effectiveness of screening programs, the data described over the past decade suggest that the observed increase in breast cancer incidence, along with the decrease in mortality and advanced-stage cases can tentatively be attributed to the impact of ongoing screening efforts and increased screening coverage[36]. New cases of cervical cancer are more prevalent in developing countries, where early diagnosis and prevention programs are limited. In Kazakhstan, cervical cancer is also a significant public health issue, with incidence rates considerably higher than those in developed countries. Population-based cytological screening was only introduced in 2008. Initially, cervical cancer screening was conducted using the conventional Pap test every 5 years for women aged 30–60. In

2017, the screening interval was shortened to 4 years, and the target age range was extended to include women up to 70 years old. Between 2008 and 2016, cervical cancer screening coverage decreased from 75.6 to 46.2% in 2012. However, after implementing an active invitation strategy in 2019, coverage increased to 83.2%. This change was accompanied by a rise in the detection of high-grade squamous intraepithelial lesions (HSIL) from 0.06 to 0.43% among women undergoing cervical cancer screening. Since 2008, the incidence of cervical cancer has increased from 17.1 to 18.7 per 100,000 women, although there is a downward trend in mortality, which has decreased from 7.7 to 6.2 per 100,000 women over 12 years[37]. Despite improvements in screening coverage and the detection of precancerous lesions, cervical cancer morbidity and mortality rates remain relatively high. It is important to note that primary prevention through human papillomavirus vaccination for cervical cancer has not been introduced in Kazakhstan. Previously, in 2014, HPV vaccination was launched as a pilot project in four sub-national regions. However, the program was halted in 2017 due to extensive media coverage about the potential or perceived side effects of the vaccine, leading to widespread parental refusal[38]. A national vaccination program is planned for the third quarter of 2024. In Kazakhstan, colorectal screening is conducted using immune analysis of fecal occult blood for individuals aged 50–70 and total colonoscopy if fecal test results are positive, with a screening interval of 2 years. Coverage of the target population varied from 78.4% in 2012 to 53.1% in 2020. Screening efforts increased the incidence of colorectal cancer from 15.5 in 2011 to 16.5 per 100,000 in 2020, while reducing mortality from 9.3 to 8.0 per 100,000 over the same period[39]. Between 2004 and 2018, the incidence rates for stages I and II colorectal cancer doubled from 35 to 67.4%, while stage IV cases decreased from 19.3 to 13.1%, and stage III cases from 45.7 to 19.5%[39].

Previously, Kazakhstan conducted screening programs for prostate, stomach, and liver cancer from 2013 to 2018. However, prostate cancer screening was discontinued owing to limited effectiveness and global debate about its contribution to mortality. Consequently, the introduction of prostate cancer screening led to increased morbidity rates without a corresponding decrease in mortality. Nevertheless, the 5-year survival rate gradually improved from 55.7% in 2013 to 62.2% in 2019[40]. Currently, screening for prostate cancer is only available for rural residents aged 55–75 years[41]. Since 2013, stomach cancer screening in the form of gastroscopy was gradually introduced in Kazakhstan, which was discontinued in 2018. In some regional studies, the results of the screening program showed a low detection rate of stomach and esophageal cancer during gastroscopy and amounted to only 8.7% of all identified primary cancer cases[42]. However, other studies showed that from 2009 to 2018, the detection of early stages of cancer (I and II) increased from 24.5 to 41.3%[43]. From 2013 to 2018, liver cancer screening in Kazakhstan was conducted by measuring alpha-fetoprotein levels in blood serum and performing liver ultrasound examinations among patients with liver cirrhosis of both sexes. The annual age-standardized incidence rate was 5.7 ± 0.1 (mean $\pm$ SE) per 100,000 for 2005–2019[44]. An analysis of this program's effectiveness in one region revealed low detection rates and low cost-effectiveness[45]. These findings may be attributed to the complexities of liver cancer screening, such as identifying appropriate risk groups, accurately diagnosing liver cirrhosis, ensuring test accuracy, and managing patients with abnormal screening results.

Our study found an increasing burden of stomach cancer and a high prevalence of cervical cancer in Almaty, while globally efforts have reduced the burden of these cancers through improved screening and prevention strategies. Cervical cancer remains one of the most common cancers among women in Almaty, highlighting the need to strengthen HPV screening and vaccination programs.

As a comprehensive measure of health that covers the burden of both fatal and non-fatal outcomes of cancers, the DALY estimates in this study can be used as a complementary and comprehensive tool for assessing population health to inform health policies and interventions. Such comprehensive assessments are scarce in Almaty as well as in the wider context of Kazakhstan and the Central Asian region. Given Kazakhstan's ongoing epidemiologic transition, the development of cancer control strategies will become increasingly important. This study used direct calculations based on cancer registry data. The DALY calculation method used in this study has the potential to be adopted for routine annual assessment of health status, interventions, and implementation of new prevention and treatment measures in the future among patients with cancer. In general, the use of national data sources opens up the possibility of basing burden of disease calculations less on modeling than in the GBD study and more on real-world data. The results can thus be better interpreted and the data quality assessed against the background of existing health care provision and systems of data collection. This also offers the possibility of sub-national analyses based on real variance in the available data; thus, the analysis could be extended to other disease groups.

Despite the strengths of this study, there are some limitations. The data collection period coincided with the COVID-19 pandemic in Kazakhstan, leading to a decline in cancer detection (from 194.7 in 2019 to 172.1 in 2020 and 191.3 per 100,000 people in 2021) and constraints on accessing treatment. This may have resulted in underestimation of the cancer burden in 2020 and 2021, necessitating further research to evaluate the pandemic's long-term impact on the national cancer burden[13]. The YLL calculation was based on life expectancy from the GBD study, which is much higher than that in Kazakhstan. Therefore, the final YLL and consequently the DALYs, as well as the share of YLL versus YLD, may be overestimated. The database of cancer cases we used did not contain information about treatment, and therefore, the sequelae of the disease. Instead, we used sequelae prevalence from the GBD database and the German Burden of Disease study. Sensitivity analysis showed a considerable impact of different severity distributions on the YLD calculations; however, this had hardly any effect on the DALYs owing to predominance of the YLL in assessing the burden of disease for cancer. Notwithstanding, the real distribution of severity in Kazakhstan and Almaty is unclear. Although the GBD study relies on modeling and not on national data, it is unclear to what extent the German distributions are transferable. Epidemiological and clinical data, which refer to the severity of disease, are therefore of particular importance for burden of disease calculations at national level. In future studies, it would be beneficial to have reliable Kazakh data available on the prevalence of cancer sequelae to provide more accurate results. In this study, we used a method to calculate YLD based on 10-year prevalence data; however, the results may differ if incidence data were applied. Although

various sources have compared these two approaches and found no significant differences, future research would benefit from comparing these methods in the context of Kazakhstan[46]. In this study, we identified data limitations that precluded the use of a longer follow-up period to assess disease trends.

Conclusion

This was the first study to assess the burden of the five most common types of cancer in the city of Almaty, Kazakhstan from 2017 to 2021. DALYs owing to these types of cancer are steadily increasing; however, morbidity and mortality rates per 100,000 tend to decrease, which indicates the effectiveness of preventive measures and management in patients with cancer. Future studies should focus on improving evaluation of the cancer burden and advancing estimation techniques in Almaty and across Kazakhstan. Critical strategies for cancer control must encompass the initiation of primary preventive measures against cervical cancer, including human papillomavirus vaccination, and the implementation of stomach cancer screening. Enhancing current prevention programs and treatment approaches, along with raising awareness about cancer and its risk factors among the Kazakhstani population, are also crucial steps.

Data availability

The data sets created and/or examined in this study are not publicly available due to restrictions imposed by the Republican Center for Electronic Health under the Ministry of Health of the Republic of Kazakhstan. The data can be obtained from the corresponding author upon reasonable request.

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Author contributions

F.K., A.R., K.K-S., D.K., N.G. designed the study. F.K., A.R., A.W., K.K-S., O.Sh, N.G. analyzed the data and performed the calculations and analyses. F.K., A.R., A.W., K.K-S., G.D., I.Zh., N.G. drafted the initial manuscript. All authors reviewed the drafted manuscript for critical content. All authors approved the final version of the manuscript.

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The authors declare no competing interests.

Ethics approval and consent to participate

Since the study had retrospective nature the need of informed consent was waived by Ethics Committee of the Kazakhstan Medical University Higher School of Public Health (No: 138 of 31.05.2021). All methods were carried out in compliance with relevant guidelines and regulations.

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Cervical Cancer Prevention in Rural Areas

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ABSTRACT

Objective: Globally, cervical cancer (CC) incidence is higher in rural areas than in urban areas that could be explained by the influence of many factors, including inequity in accessibility of the CC prevention measures. This review aimed to identify and analyze factors associated with a lack of cervical cancer screening and HPV vaccination programs in people living in rural areas and to outline strategies to mitigate these factors.

Methods: The literature search encompassed two focal domains: cervical cancer screening and HPV vaccination among populations residing in rural areas, covering publications between January 1, 2004 to December 31, 2021 in the PubMed, Google Scholar, Scopus, and Cyberleninka databases, available in both English and Russian languages.

Result: A literature review identified 22 sources on cervical cancer screening and HPV vaccination in rural and remote areas. These sources revealed similar obstacles to screening and vaccination in both high and low-income countries, such as low awareness and knowledge about CC, screening, and HPV vaccination among rural residents; limited accessibility due to remoteness and dearth of medical facilities and practitioners, associated with a decrease in recommendations from them, and financial constraints, necessitating out-of-pocket expenses. The reviewed sources analyzed strategies to mitigate the outlined challenges. Possible solutions include the introduction of tailored screening and vaccination campaigns designed for residents of rural and remote locations. New screening and vaccination sites have been proposed to overcome geographic barriers. Integrating HPV testing-based CC screening is suggested to counter the lack of healthcare personnel. HPV vaccination is essential for primary cervical cancer prevention, especially in rural and remote areas, as it requires less medical infrastructure.

Conclusion: Certain measures can be proposed to improve the uptake of CC screening and HPV vaccination programs among rural residents, which are needed to address the higher prevalence of CC in rural areas. Further investigation into cervical cancer prevention in rural and remote contexts is necessary to ascertain the optimal strategies that promote health equity.

INTRODUCTION

Globally, cervical cancer (CC) ranks 5th among the major cancer sites [1]. According to the World Health Organization (WHO) in 2018 the age-standardized incidence of CC ranged from 75.0 per 100,000 women in high-risk countries to less than 10.0 per 100,000 in low-risk countries. The World Health Organization has determined that if the incidence drops to four cases per 100,000 women, CC will no longer be considered a public health problem. With this purpose, in 2020 the WHO presented a strategy, which listed three indicators to be achieved by member countries by 2030: 90% vaccination coverage of girls aged less than 15 years; 70% screening coverage of women aged 35–45 years with high-precision tests; and 90% provision of medical care to women diagnosed with cervical disease (both precancerous alterations and established cancer) [2]. Primary CC prevention covers vaccination of adolescent girls against human papillomavirus (HPV) and screening of women for the presence of dysplastic (precancerous) cites in the uterine cervix.

Population-based screening with the help of HPV testing (Co-test) is perhaps the most effective, but the most resource consuming approach both in terms of financial resources and qualified medical professionals [3]. However, each country selects approach depending on healthcare capacities. It has to be noted that effectiveness of screening programs varies with the level of population engagement (coverage and commitment). It was estimated that in order for a screening to be efficient, at least 70% of the target population has to be covered. This level is not always attained as for a variety of reasons many countries do not cross the 50% threshold [4–5].

Cervical cancer incidence varies not only with geographic area, but also with the place of residence. Such, the disease is 15% less common in urban areas as compared with the rural. Cities also experienced a more notable decline in the cancer incidence (10.2% vs. 4.8% in the rural area). The greatest difference was found in the incidence of cancers associated with modifiable risk factors, like tobacco smoking, HPV infection, and availability of screening programs [6]. Besides, rural populations often face disparities in terms of cancer prevention strategies, which is manifested by lower coverage with both CC screening and HPV vaccination [7]. The reasons for this disparity are complex and may include:

1. geographical and socio-economic barriers in obtaining medical care
2. lack of recommendations from the side of medical workers
3. low awareness of cervical cancer and HPV infection
4. low awareness of and commitment to screening for CC and HPV vaccination
5. socio-cultural barriers against application for gynecology services and vaccination of girls
6. limited access to diagnostic and curative services for pre-malignant conditions, etc [8].

Commitment of women residing in rural areas to get CC screening is most weak in rural areas, since women are often unaware about the potential threats of CC. It has to be noted that people residing in rural areas may be socioeconomically deprived and have inadequate hygiene standards and poor sanitation. Also, women living in rural areas may be exposed to other risk factors, like early marriages and multiple pregnancies, which make them more susceptible to CC. Moreover, many rural areas around the globe face a lack of medical and social facilities and this limits the possibility of obtaining sound advice and guidance. Under such conditions, various strategies to improve screening, like establishment of rural cancer registries, have proven useful in minimizing the magnitude of this public health problem [6]. The implementation of self-sampling for HPV DNA testing, as opposed to traditional cytological screening, has the potential to significantly impact the challenge of improving cervical cancer screening coverage in rural areas [9]. Thus, this review is aimed at comprehensive analysis of the range of issues related to the primary and secondary prevention of CC in rural areas of the world, including CC screening and HPV vaccination.

MATERIALS AND METHODS OF RESEARCH

SEARCH STRATEGY

To meet the review aim, a thorough search of literature was carried out in the following databases: Scopus, PubMed (Medline), Google Scholar, and Cyberleninka. The search strategy aimed to identify relevant studies regarding cervical cancer screening and human papillomavirus (HPV) vaccination in rural areas. Search parameters were limited to studies published between January 1, 2004 and December 31, 2021 The search strategy utilized a combination of Medical Subject Headings (MeSH) terms, including ["Uterine Cervical Cancer" (MeSH)] and ["Cancer Screening Test" (MeSH)] or ["Human Papillomavirus Vaccine (MeSH)], and ["Rural Population" (MeSH)]. No restrictions were imposed regarding the selection of countries or their income levels. The list of selected studies was composed and checked for the presence of duplicates, which were eliminated.

STUDY SELECTION AND SCREENING

The initial screening process began with a review of the titles of retrieved papers to determine their relevance to the scope of this review. The search included studies where the study participants were people living in rural or remote areas, and the design of these studies was descriptive, including qualitative and quantitative methods, observational, and interventional with the evaluation of educational interventions. Exclusion criteria encompassed unavailability of full text or full text in languages other than English or Russian, content falling outside the scope of the review's aim, publications outside the specified time frame, and studies with poor methodological quality, such as commentaries, editorials, case reports, and correspondence letters. Subsequently, abstracts were retrieved and evaluated to confirm if a study met the inclusion criteria (Table 1). Next, the papers' abstracts were obtained and it was ascertained that they: (i) reported the utilization of CC screening conducted among women aged 9 and 70 years old; (ii) evaluated the HPV vaccination related issues; (iii) focused on population residing in rural areas; and (iv) published in English or Russian languages.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Original papers describing all methods of CC screening in rural areas among women aged 20 to 70 years old	Studies falling outside the scope of the review's aim.
Original papers describing HPV vaccination in rural areas	Studies examining CC screening and HPV vaccination without the place of residence specification
Articles published between January 1, 2004 to December 31, 2021	Studies on HPV vaccination among boys
Full text articles	Studies examining HPV infection
	Studies investigating vaccines other than HPV
	Unavailability of full text studies
	Duplicate of papers

Table 1 Inclusion and exclusion criteria of study selection.

Studies failing to fulfill the inclusion criteria were excluded. Article selection flowchart is presented in Figure 1.

The initial search from the databases included 838 articles. Following duplicate removal 607 were eligible for the screening process, and a total of 22 articles fulfilled the study criteria and were included in this review. The resulting manuscript was structured in a form of narrative review and was discussed between all co-authors.

Given the study's design and objectives, it wasn't feasible to conduct a comparative analysis of cervical cancer prevention challenges in urban and rural areas, which could be a potential limitation, as densely populated urban regions in some countries might share similar constraints
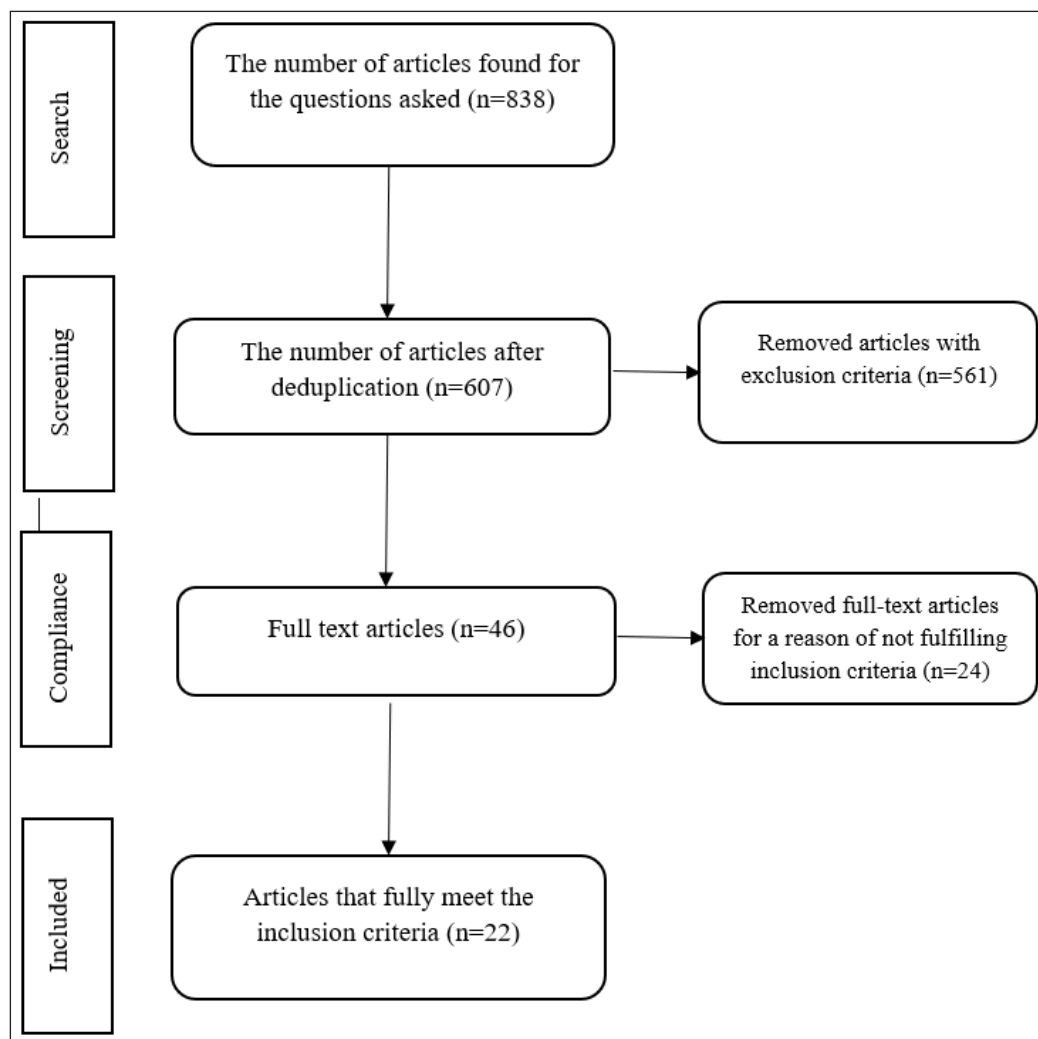
Figure 1 Article selection flowchart.

in accessing screening services with women in rural areas. This review analyzed the prevalent barriers encountered by cervical cancer prevention initiatives in rural and remote regions across diverse countries with varying capacities. A potential limitation of this study is that the proposed solutions may not universally apply to diverse settings.

International experience on implementation of CC screening programs in rural areas

Nowadays, CC screening programs are actively implemented and widely used by different healthcare systems across the globe. Nevertheless, these screening programs are not always successful as they are dependent on such factors as population adherence and coverage. Meanwhile, it is important to measure the population adherence since it can help to identify "weaknesses," the spots of non-effectiveness, to overcome them. Besides, interventions targeted on elimination of inequalities must be envisaged and for this, inequalities need to be defined and traced. Addressing the issue of inequality in CC screening availability concerning residential location, service accessibility, and economic standing of regions, it is essential to consider that a primary approach to enhance CC screening program coverage within low-resource settings involves transitioning from routine cytological CC screening (Pap test) to self-sampling and HPV DNA testing, which is a more cost-effective method. This transition aligns with the recommendations by the WHO for CC screening [10].

There is a range of international studies investigating the problems associated with implementation of CC screening programs in rural areas and proposing possible solutions (Table 2).

AUTHORS (YEAR OF PUBLICATION)	COUNTRY	STUDY POPULATION	TYPE OF CC SCREENING	STUDY DESIGN	KEY FINDINGS	PROPOSED SOLUTIONS
Liu et al (2017) [9]	China	Women aged 35–64 years	Population-based cervical cancer screening (National Cervical Cancer Screening Program in Rural Areas)	Survey	The vast majority of women (96,0%) expressed positive attitudes towards screening. Still, many respondents reported low awareness of the screening program, and more than a third (36,3%) had never taken part in the program	Information campaigns among target population group. Teaching medical personnel about C identification via screening. Mechanisms to ensure the continuity of health education should be envisaged.
Thompson et al (2017) [14]	Latin America	3 years after the age of initiation of sexual activity	Population-based cervical cancer screening	Randomized controlled trial with educational interventions	Women living in rural areas, low socioeconomic status and high enclave areas have 12.7 times higher rates of invasive CC than those who live in areas of high socioeconomic status and low enclave areas. More than 60% of late-stage cancers are found in the areas with low health care and under-examined groups of women.	women residing in rural areas
Ndejjo et al (2016) [24]	Uganda	Women aged 25–49 (VIA, 3 years); 30–49 (HPV)	National Cervical Cancer Screening recommendations	Survey	Of the 900 women, only 43 (4.8%) had ever been screened for CC. Barriers to cervical cancer screening were negative individual perceptions 553 (64.5%) and health facility related challenges 142 (16.6%).	Increase access to cervical cancer screening in rural areas and engage health workers to discuss the CC disease with women.
Ruddies et al (2020) [22]	Ethiopia	Women aged 30–49 years	No organized or opportunistic cervical cancer screening program	Survey	Only eight women (2.3%) had been screened before. Although 240 women (70.4%) had the intention to be screened, only 107 (31.4%) said that they had access to a screening facility. Living in an urban setting made it 3.35 times more likely to have a positive attitude towards cervical cancer screening as compared with women living in rural areas.	Special emphasis should be put on training of health care providers with a focus on cervical cancer and its screening,
Rosser et al (2015) [29]	Kenya	Women aged 25–49 (VIA, 5 years); 25–30 (cytology, 5 years); 30–49 (HPV test, 5 years)	National Cervical Cancer Screening Program. Pilot implementation of self-sampling HPV testing	Survey	The main obstacles in providing services were a lack of sufficient staff (62%), inadequate training or a shortage of trained personnel (60%), low staff motivation (25%), insufficient space for screening activities (35%), and difficulty with supplies (31%) or autoclaving (9%). Also, low community mobilization as a problem within the population	Additional health care providers training, increased community mobilization by educational campaigns and training for both groups
Gottschlich et al (2021) [30]	Guatemala	Women aged 25–29 (cytology, 3 years); 50–54 (cytology, 3 years); 30–49 (cytology, 3 years); 30–39 (HPV test, 5 years); 40–49 (VIA, 3 years)	National Cervical Cancer Screening Program.	Qualitative, in-depth interview	Barriers to screening included ancillary costs, control by male partners, poor provider communication and systems-level resource constraints, like shortages of tests and long wait times	Discussions with women who have been screened for cervical cancer, health campaigns, self-screening for HPV

Table 2 International experience on implementation of CC screening programs in rural areas: major problems and possible solutions.

East China is one of the places with a heavy burden associated with CC. Although the Chinese government continuously provides affordable, free CC screening to women residing in rural areas aged 35–64 years, the program has low coverage even in more developed parts of East China. The authors posit that a lack of awareness regarding CC screening among women residing in rural areas constitutes the primary issue leading to inadequate coverage. Furthermore, they underscore the pivotal role of healthcare workers in mitigating this challenge. The main problem affecting low attendance in screening is low awareness of the existing screening program. According to the results of this study, over a third of women living in rural areas have never participated in cervical cancer screening. However, the overwhelming majority of women in rural areas have a positive attitude towards screening. Another important factor is the role of healthcare workers, as they contribute to health promotion and provide information about CC and CC screening. Thus, the knowledge of medical professionals about CC is very important since they have to provide accurate and up-to-date information to women. Therefore, it was proposed to target the primary healthcare professionals with upgraded training on a range of issues related to CC. In addition, different approaches to ensure the continuity of health education should be studied and implemented, as one short speech on health issues may not transform into improved screening attendance. Despite the fact that education-oriented approach is relatively costly and time consuming, it is likely to have a long-lasting impact, which will manifest as reduced mortality and improved survival of CC patients [11].

Certain Latin American countries demonstrate the highest incidence and mortality rates from CC (9.4 and 2.6 per 100,000 people, respectively). These numbers even surpass the data observed for Afro-American population (8.9 and 3.9 per 100,000 people, respectively) [12–13]. Perhaps, one of the contributing factors to this alarming situation is a relatively low level of CC screening in rural areas of Latin America. Such, those Latin American women who live in rural areas, have 12.7 times higher rates of invasive CC than those who are living in areas of high socioeconomic status [14]. Also, more than 60% of late-stage cancers are found in the places with low level of healthcare provision, which is common for rural regions [15]. Consequently, Latin American women of lower educational and socioeconomic status living in rural areas and enclaves are significantly less likely to be screened for CC than other Latin American women. Bearing in mind that the proportion of rural population in Latin America is high, there is a need to increase adherence to CC screening appointments among rural communities, which could be done via introduction of educational interventions that are grounded on the "promoter" program [12].

There is definitely a need for specific, clear policy measures targeted at raising the CC screening coverage among rural populations. For this, certain interventions could be proposed which address each of the sensitive issues: reaching those who are underserved, increasing awareness of target population groups and sensitizing policy makers on these issues. As a result, several different strategies have been suggested to improve the screening behavior. These strategies include preparation and sending of reminders, provision of various educational campaigns [16–17], elimination or reduction of structural and financial barriers [18], and activities aimed at improving knowledge of CC screening among the medical professionals. Besides, it is worth developing recommendations on the use of individualized educational interventions, to encourage and motivate women to undergo the CC screening [19–20] and specifically adapt all interventions to the needs of specific population groups.

The HPV self-sampling campaign implemented in Bolivian rural regions effectively elevated screening coverage, achieving the annual average within a mere three-month period [21].

Therefore considering the constraints of limited resources, it is advisable to explore alternatives to routine cytological screening, as suggested in the recent WHO recommendations: implementation of HPV DNA testing and self-sampling as the preferred methods in remote and rural areas [9].

Peru exhibits a high incidence of cervical cancer, also, there is a low level of CC screening coverage. In Peru inadequate screening is due to low public awareness of cervical cancer and the HPV vaccine. This study emphasizes medical professionals' views, highlighting the negative perception of healthcare services and the absence of a culture of preventive examinations by population. Addressing the issue of limited coverage necessitates educational initiatives in rural Andean Peru. These campaigns are indispensable for increasing awareness about cervical cancer (CC) and its screening, employing materials that align with the cultural context [22].

Additionally, another study conducted within a rural population in Mexico emphasized organizational obstacles to cytology screening, including irregular material supply, distant clinic location, and inadequate communication between staff and patients. Women were provided with the option of self-sampling for HPV. Participants perceived this approach as simpler, less embarrassing, and less painful than cytology. Shifting to HPV self-testing rather than cytology may mitigate certain gender, organizational, or technical quality of care concerns [23].

Several studies conducted in rural areas of African countries such as Uganda, Malawi, Ethiopia and Kenya have also identified major barriers to CC screening. Cervical cancer poses a significant threat to women's health in Uganda. In 2010, Uganda launched a strategic plan to prevent and manage cervical cancer. However, in rural areas, CC screening coverage remains low due to limited awareness, healthcare challenges, individual perceptions, lack of visible symptoms, low risk perception, time constraints, and test result apprehensions. To address these challenges, improving access to cervical cancer screening in rural areas and engaging healthcare professionals in proactive discussions with women, emphasizing screening awareness, thus increasing their adherence to CC screening, is crucial [24].

A study conducted in Malawi found that the main barriers to CC screening were low knowledge, perceived low susceptibility. Study participants did not perceive CC screening as essential healthcare and typically underwent screening when seeking medical assistance for gynecological issues. It is essential for healthcare providers to prioritize improving patients' understanding of cervical cancer and their capacity to evaluate their individual risks. Moreover, consistent support and active promotion of cervical cancer screening are of paramount importance. These measures could present an optimal solution to the issue of cervical cancer (CC) screening in rural Malawi [25].

Ethiopia is one of the developing countries where cervical cancer has high incidence and mortality rates, and access to screening and treatment, knowledge about HPV and cervical cancer is limited. These barriers contribute to women's low susceptibility to cervical cancer, which in turn is reflected in inadequate screening practices. Among Ethiopian women in rural areas, a positive attitude towards screening is formed by the influence of socio-demographic factors. Often, women with a higher level of education, who are aware of cervical cancer and use contraceptives, have a higher adherence to screening. It should be noted that educational interventions are needed in rural Ethiopia regarding adequate information on risk factors, screening and its availability. Considering that medical personnel are the main source of information about cervical cancer and its screening, it is very important to conduct their continuous training in these matters [26]. Another study conducted in Ethiopia emphasized the introduction of HPV self-sampling as a significant solution to address the challenges of accessibility and low coverage in cervical cancer (CC) screening. To enhance its effectiveness, the authors emphasize the importance of raising awareness, mobilizing the community, and involving families in this process [27]. In Kenya, the main problems of low coverage include inadequate staffing, a shortage of adequately trained personnel or insufficient training, limited staff enthusiasm, inadequate facilities for screening and difficulties in obtaining supplies or performing autoclaving [28]. The solutions to these problems include additional health care providers training, increased community mobilization by educational campaigns and training for both groups [29]. In Guatemala, the scarce availability of efficient screening and treatment options has led to significantly elevated rates of cervical cancer incidence and mortality. A study conducted in Guatemala, assessing the integration of HPV self-sampling, indicates that introducing this program in low-income populations, particularly within predominantly indigenous and rural communities, could enhance engagement with established cervical cancer screening programs [30].

Vaccination against human papillomavirus in rural areas

Although CC screening program requires significant infrastructural and organizational investments, HPV vaccination sets fewer logistical demands on the healthcare system than repeated screening, testing, and treatment for cervical disease. This approach is considered to be extremely important in the light of the primary prevention of CC in rural areas.

However, provision of HPV vaccination to the rural population is associated with certain difficulties that result low coverage. Such, when comparing coverage with HPV vaccination in the United States

it was found out that the chances of starting vaccination were lower in the villagers by almost 15% as compared with the urban dwellers [31]. In rural areas it is important to set diverse strategies to overcome geographical, communicational, and other barriers at various levels: patient, medical organizations, community, state, and country. Such measures include changing and adapting organizational processes, evaluating the performance of individual clinics and healthcare workers, provision of educational programs, setting up vaccination in schools, pharmacies, and public places. Besides, for a HPV vaccination program to be effective, local characteristics have to be taken into account to adapt communication strategies and this necessitates research on what works especially well in rural areas [8].

Numerous studies have confirmed the relationship between the level of HPV awareness, its association with CC, knowledge about availability of effective vaccine, and the intention to be vaccinated among various populations. It was not surprising that better awareness was associated with higher levels of education and older age [32–35]. The place of residence also plays role and such, for example, in the Mysore region of India urban parents were more than twice as knowledgeable about HPV, CC, and HPV vaccinations as rural parents [36]. Another study from China has shown that urban residents had heard about HPV much more often than the rural residents (39.1% vs. 27.1%, respectively). Also, they were better informed about the HPV vaccine (23.7% vs. 15.1%, respectively). Moreover, women with a higher knowledge more often expressed a positive opinion about vaccination [37].

An interview-based study from Malaysia found an extremely low knowledge of women residing in rural areas aged 18–25 years about HPV, cervical cancer, and the vaccine. This knowledge was so low that an average score equaled 2.4 points out of 14. The intention to be vaccinated was associated with awareness of screening and CC risk factors [38]. Similar data were obtained in a study coming out from a rural area in China's Hong Nan province, where 58.8% of women aged 20–45 years showed the intention to be vaccinated. Older age and higher educational level were associated with the intention to be vaccinated and women who were aware of the HPV vaccine and that CC is a preventable disease, expressed the desire for vaccination two times more often than those who were not informed. Meanwhile, women who had never heard of the vaccine and were worried about the possible side effects were more likely to refuse vaccination [39]. Several studies from the USA also confirmed the fact that rural residents are less informed about HPV and HPV vaccination [40–41].

The studies conducted in the Commonwealth of Independent States show that local parents are often vaccine hesitant, and this impacts vaccination uptake rates which are especially low in rural areas. For instance, in Russian Federation rural parents are more likely to refuse vaccines as compared with the urban parents (17% vs. 12%) [42]. In the Republic of Kazakhstan, there is low awareness of parents about availability of HPV vaccines (66% ever heard about this) and medical workers and the Internet serve as the main information sources. Like in case with China, a positive decision to vaccinate against the HPV was associated with older age and higher level of education. Nevertheless, there were no significant differences in awareness of HPV and the HPV vaccines among rural and urban residents [43]. Another study from Kazakhstan also failed to reveal the relation between the place of residence and parental vaccine hesitancy [44]. Table 3 summarizes the major finding of international studies on the knowledge of HPV vaccination in different population groups.

Sources of information used by rural people to get knowledge about cervical cancer, HPV, and HPV vaccination

Since many studies reported low levels of awareness about strategies used to prevent CC, it is necessary to focus on the sources of information used by different people in order to increase their vaccine literacy. In rural areas of Cambodia, the media, i.e., radio and television, was recognized to be the most common information source (39%). The reason behind this is the availability of radio and TV sets at homes, which underlines the undoubted importance of disseminating health information through these sources. Much less often, the villagers received information from medical workers or medical organizations (10%) [45]. A study performed in the rural areas of Bangladesh also demonstrated that the media is the most popular information source (53.4%), followed by medical professionals (35.3%), the Internet and social networks (30.4%), family members (23.7%), friends and neighbors (14.5%) [46]. Female residents of villages in China named medical workers as the most trusted source of information (58.8%), and thereafter were called WeChat, microblogs, TV programs, and the Internet [39].

AUTHORS (YEAR OF PUBLICATION)	COUNTRY	STUDY POPULATION	STUDE DESIGN	AWARENESS ABOUT HPV VACCINATION SS
Ping Wong et al (2010) [38]	Malaysia	Young women residing in rural areas in Malaysia were interviewed using a standard questionnaire (N = 449).	Survey	The mean total knowledge score (14-item questionnaire) was 2.37 (SD±1.97). Although many respondents never heard of the HPV vaccine, two-thirds professed an intention to receive the HPV vaccine. Intention to receive the vaccine was significantly associated with knowledge of cervical screening and cervical cancer risk factors.
Thomas et al (2012) [58]	USA	African American parents or caregivers with children 9–13 years of age completed a survey (N = 400).	Survey	Perceived vulnerability (knowledge about HPV) constituted 40.4%, while perceived severity (awareness that HPV can cause a CC) equaled 45.6%.
Feng et al (2012) [37]	China	Women attending the checkup clinics were invited to complete a questionnaire-guided interview (N = 1432).	Qualitative, interview	39.1% of women living in urban areas and 27.1% of women in rural areas were aware about HPV, whereas 23.7% and 15.1%, respectively, heard of the HPV vaccine. The mean score of HPV knowledge was 3.75 in residents of urban areas and 3.18 in residents of rural areas.
Blake et al (2015) [59]	USA	National Cancer Institute's 2013 Health Information National Trends Survey of USA adult, civilian, non-institutionalized people (N = 3185).	Survey	People living in rural areas were significantly less likely to know that HPV causes cervical cancer as compared with those living in urban areas.
Nasritdinova et al (2016) [43]	Kazakhstan	Population of four regions of Kazakhstan took part in anonymous survey (N = 5338)	Survey	66% of respondents were aware about existence of HPV vaccine. No significant difference between urban and women residing in rural areas was detected.
Boyd e al (2018) [41]	USA	Vaccinated and non-vaccinated adolescents aged 11–18 years and their caregivers from three rural counties of south Alabama participated in individual interviews (N = 48).	Qualitative, interview	75% of caregivers and 33% of adolescents heard about HPV and 62.5% of adolescents were aware that HPV can lead to cervical cancer as compared with 55.6% of the caregivers. 60% of caregivers of non-vaccinated adolescents and 33.3% caregivers of non-vaccinated adolescents heard about the HPV vaccine.
Mohammed et al (2018) [40]	USA	Respondents older than ≥18 years completed the Health Information National Trends Survey 2013–2017 (N = 10147).	Survey	55.8% and 58.6% of rural residents were aware of HPV and HPV vaccine, respectively. As compared with urban residents, rural residents were less likely to be aware of HPV and HPV vaccine. Rural residents were less likely to know that HPV causes cervical cancer, and that HPV can be transmitted through sexual contact.
Degarege et al (2018) [36]	India	Parents of school-going adolescent girls completed a self-administered questionnaire (N = 1609).	Survey	Urban parents were more likely to believe that both HPV infection and CC could cause serious health problems. Parents' belief that HPV vaccination will make girls sexually active was lower among urban parents as compared with rural. There was no significant difference between urban and rural parents in beliefs about susceptibility of their daughters to HPV infection or cervical cancer, and beliefs about the safety and ability of HPV vaccine to protect against cervical cancer.
Touch and Oh (2018) [54]	Cambodia	Women aged 20–69 years who lived in Kampong Speu Province participated in the survey (N = 440).	Survey	Only 2% of women were aware that HPV infection is a risk factor for cervical cancer; 8.6% of women were aware that HPV is a sexually transmitted infection; 35.2% of women knew that cervical cancer can be prevented by vaccination; and 62% of women were willing to receive vaccination for themselves as well as for their daughters.
Qin et al (2020) [39]	China	Women aged 20–45 years from rural areas of Hunan Province in China completed the anonymous self-administered questionnaire (N = 2101).	Survey	21.6% of women were aware of HPV as a risk factor of CC and 50.28% of women knew about HPV vaccine.
Banik et al (2020) [46]	Bangladesh	Women of reproductive age living in rural areas of Bangladesh were interviewed with a semi-structured questionnaire (N = 600).	Survey	55.2% of respondents identified HPV infection as a risk factor for CC, and 48.3% knew that HPV vaccine can prevent CC.
Kadian et al (2020) [60]	India	Women of urban and rural background aged 18–65 years completed the questionnaire (N = 1500)	Survey	55% of women had little knowledge about cervical cancer, and 87.5% were informed about HPV infection, while 95% were aware about HPV vaccine. Good knowledge about HPV infection and HPV vaccination was very low in both rural (6.25% and 1.25%, respectively) and urban (14.3% and 4.3%, respectively) areas.

Table 3 Knowledge of HPV and HPV vaccination in rural different population groups across the globe.

Lack of advice from the side of health workers is one of the main reasons for the decline in vaccination coverage in rural areas of the United States and this includes inappropriate notification [47–48]. The advice of a qualified health professional plays a significant role for parents when making decision on vaccination of their children. It has been proven that a strong recommendation from a doctor can increase the level of vaccination uptake by three to nine times [49]. It has to be recognized that rural healthcare experiences a shortage of medical staff and when this is coupled with a substantial heterogeneity of patients, it leads to the insufficient knowledge about adolescent immunization. Still, rural population tends to trust the doctor's opinion more than urban [50].

In the Russian Federation, a great proportion of rural parents trust their local doctors (91.7%), but 71.2% of them expressed the need for additional information. Similar findings were obtained in the Kyrgyz Republic, where 72.8% of rural mothers trust the opinion of doctors, but they also were willing to receive additional information [51]. In the Republic of Kazakhstan the level of trust in medical workers expressed by parents when making decision about mandatory childhood vaccinations was 68.1% among those who agreed to vaccinate, while those who refused to do so, trusted the Internet more [44]. Table 4 in Supplementary Materials presents the main findings on the sources of information about HPV vaccination used by members of different communities across the globe.

Availability of infrastructure for the HPV vaccination in rural areas and considerations about the cost

Lower coverage rates with the HPV vaccination in rural areas can also be attributed to the lack of access to transportation, which occurs in both developed and developing countries. Such, in the United States rural parents often delay vaccination because of transport inaccessibility [45]. Likewise, developing countries of Africa face the problem with transport accessibility as one of the existing barriers for vaccination, which is significantly more pronounced in rural areas than in the cities (27% vs. 12%) [52].

Depending on the possibilities available within the country, different countries solve this problem in different ways. The problem of transportation to healthcare facilities for the HPV vaccination can be overcome in the following ways: provision of vaccination in schools, pharmacies, dental clinics, arrangement of mobile vaccination clinics, involvement of social workers, and development of navigation schemes for parents.

Although setting a vaccination program in a medical facility has clear advantages that are related to the provision of quick assistance when needed as well as advice from qualified medical personnel, this is not always possible in rural areas. Thus, in the United States it was proposed to provide vaccination in rural pharmacies. The rationale behind this decision is that pharmacists often enjoy the same level of trust from local residents as other medical professionals do and are the most accessible. This is, in particular, due to their proximity, a wide network of pharmacies across the country, convenient opening hours, and absence of the need to make an appointment in contrast with the clinics. A vaccination program on the basis of an existing pharmacy network can help to overcome the structural barrier at the patient level, which also includes lack of time, financial restraints, and unavailability of transportation. Of interest is the fact that an interview-based study on caregivers of adolescents in rural areas of the United States demonstrated a low awareness about the possibility to get vaccination in local pharmacies. Still, most respondents considered a pharmacy to be a more convenient place for vaccinations, which saves their time and money [53].

Another structural barrier for the HPV vaccination in rural areas is the cost. The HPV vaccine is still one of the most expensive vaccines available. Despite significant reductions in vaccine prices for low- and middle-income countries, the cost remains prohibitively high with considering additional expenditures imposed on residents of rural and remote areas. For instance, the rural population of Cambodia showed high motivation for the HPV vaccination, but lack of knowledge and the vaccine cost have become the major barriers for uptake of the HPV vaccine [54]. The study carried-out in rural Bangladesh also found a high level of intention to get vaccinated, but vaccination coverage remains extremely low (5.3%). Like in case with Cambodia, the main reasons for this phenomenon are the high cost of vaccine (40.1%) and the lack of knowledge (34.3%) [46].

The full economic cost of the vaccination program includes the cost of the HPV vaccine, but also other costs associated with the program planning, staff training and mobilization, delivery of the vaccine, organization of storage, and provision of cold chain. These costs make up about 47% of the total economic cost [55]. In this regard, an important role in achieving optimal coverage is played by the financial availability of vaccination, in particular, full coverage at the expense of the state or insurance companies. However, in several countries vaccination against HPV is carried out on a paid basis, which is certainly an obstacle to obtaining a desirable level of vaccination among the population. The study from Vietnam showed that rural residents were almost 10 times more interested in vaccination than city dwellers. However, after the vaccination price was articulated, the desire to get vaccinated decreased dramatically [56]. The study from rural China found out that 8.5% of women cited high costs as a barrier to vaccination [39].

Meanwhile, financial support for low- and middle-income countries could be provided by the Global Alliance for Vaccines and Immunizations (GAVI), sponsored by some governments and private foundations. By 2019, 19 countries (35% of all middle- and low-income countries) received financial support from the GAVI. Funding comes from a grant whereby the cost of the vaccine for a cohort of nine-year-old girls could be as low as 2.40 United States dollars in the first year of vaccine introduction and the grant also covers necessary staff training. In addition, during the first year, the Alliance covers the costs of vaccination of a cohort of girls aged 10–14 years [57]. Figure 2 presents a summary of strategies that could be implemented to overcome infrastructure and cost-related barriers in rural areas.
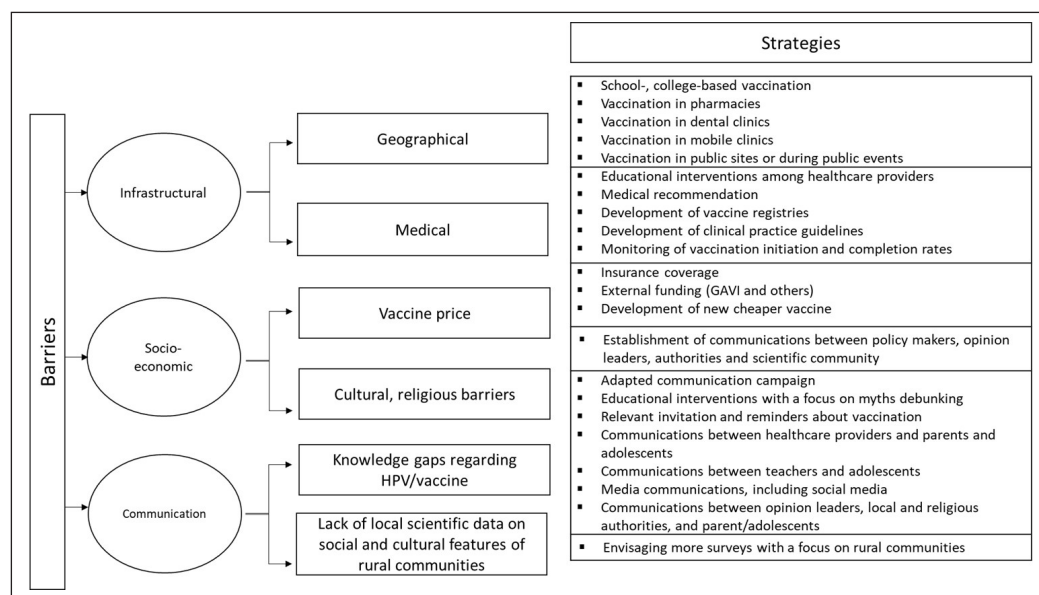
Figure 2 Strategies to overcome the infrastructure, communication, and cost-related barriers in rural areas.

CONCLUDING REMARKS

There are substantial inequalities in access to and uptake of CC screening and HPV vaccination between urban and rural populations. This may be explained by unavailability or inaccessibility of medical services, lower socio-economic status, and medical ignorance, which exist in many countries and are particularly common among the rural population. Nevertheless, certain interventions could be proposed to improve the CC prevention programs in the rural areas and these include conducting widely implementation of HPV DNA testing (including self-sampling testing), educational interventions among the target groups of women and healthcare professionals involved in CC screening and HPV vaccination programs. Besides, there is a need to increase availability of the HPV vaccination by means of subsidizing the vaccine cost, but also raising awareness of the rural population and improving accessibility through the provision of shots in proximity to the place of residence.

ADDITIONAL FILE

The additional file for this article can be found as follows

- **Supplementary Materials. Table 4.** Sources of information about CC, HPV and HPV vaccination as reported by members of different communities. DOI: https://doi.org/10.5334/aogh.4133.s1

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

IZ, FK, and NG developed the concept. Sh, NG, YS contributed to the design of the research. IZ, FK performed a literature search. IZ, FK, YS wrote the manuscript. All authors commented on earlier drafts and read and approved the final manuscript.

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Developing HPV Vaccination Communication Strategies: Assessing Knowledge, Attitudes, and Barriers Among Healthcare Professionals in Kazakhstan

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Abstract: Background: Cervical cancer, predominantly caused by human papillomavirus, remains a major public health issue globally and in Kazakhstan, where it ranks among the most common cancers in women. A pilot HPV vaccination programme in Kazakhstan was suspended in 2017 due to mass parental refusals, and it is planned to be restarted in the coming years. This study aims to assess the knowledge, attitudes, barriers, and sources of information about HPV and the HPV vaccine among healthcare professionals in Kazakhstan. Methods: A cross-sectional study (December 2022–May 2023) involving 1189 healthcare professionals in Kazakhstan used a self-administered questionnaire. Statistical analysis included descriptive statistics, mean knowledge score, between-group comparisons, and binary logistic regression to identify factors linked to higher knowledge and vaccine recommendation. Results: The study found that the average knowledge score for HPV and the HPV vaccine among participants was 11 out of a possible 18. Correct answers to the questionnaire were observed more frequently among physicians than among nurses ($p < 0.001$). In our study, 72.6% of healthcare professionals expressed a positive intention to recommend the HPV vaccine. The likelihood of recommending the HPV vaccine was significantly higher among those with higher knowledge of HPV and its vaccine (OR 1.8; 95% CI 1.3–2.5; $p < 0.001$), those familiar with cervical cancer patients (OR 2.0; 95% CI 1.5–2.8; $p < 0.001$), and those with positive attitudes towards the COVID-19 vaccine and childhood vaccination (OR 2.3 and 1.5, respectively). Healthcare professionals identified key barriers to HPV vaccination, including public mistrust (49.4%), fear of side effects (45.9%), and insufficient knowledge among healthcare professionals themselves (30.3%). Information from the internet, including articles and journals, was the most commonly used source of information, followed by social media and colleagues. Conclusions: The disparities identified call for a tailored, multifaceted communication strategy that addresses the diverse needs of health professionals to address the differences in awareness between different groups, in order to ensure successful implementation and coverage of HPV vaccination across Kazakhstan.

1. Introduction

Cervical cancer (CC) was the fourth most common cancer among women, with an estimated 604,127 cases and 341,831 deaths worldwide in 2020, mostly in developing countries due to limited access to early detection and prevention [1]. In Kazakhstan, CC ranks second among all cancers in women, with an age-standardised incidence of 15.7 and a mortality rate of 7.2 per 100,000 women. [2]. Persistent infection with high-risk human papillomavirus types (HR-HPV) is a major factor associated with the development of CC and oropharyngeal, anal, penile, vaginal, and vulvar malignancies in women and men. HPV-associated cancers account for 5.2% of all cancers worldwide and an average of 8.0 per 100,000 person-years, with up to 80% of cases attributable to cervical cancer [3]. According to GLOBOCAN, the incidence of HPV-associated cancer types in Kazakhstan in 2020 included more than 3300 new cases [4]. In addition to malignant neoplasms, HPV types with low oncogenic risk cause benign diseases such as condylomatosis, and papillomatosis of the genital, oropharyngeal, and laryngeal areas in adults and children, significantly affecting health and quality of life and increasing costs for patients and the healthcare system. The prevalence of HPV varies between regions and populations, with a global average prevalence of 32.1% [5]. In Kazakhstan, the prevalence of HPV infection among women is significant, ranging from 39.1% to 55.8%, with one of the most common types being HPV 16 [6,7]. The prevalence of HPV in men worldwide is also high, at 31% for any HPV and 21% for HR-HPV [8].

Primary prevention of HPV-associated disease has been possible since the introduction of the first HPV vaccine in 2006 [9]. HPV vaccination, initially recommended for girls, has been extended to boys in several countries. Implementing a universal, gender-neutral vaccination strategy strengthens herd immunity, advances the goal of eliminating cervical cancer, prevents HPV-related cancers in men, promotes gender equality, and reduces stigma and misinformation associated with the vaccine [10]. Cervical screening and HPV vaccination, combined with timely treatment, make cervical cancer almost completely preventable [11]. In 2013, a pilot, school-based HPV vaccination programme for girls aged 12–15 years in four regions was launched in Kazakhstan, but it was discontinued in 2017 [12]. The Ministry of Health of Kazakhstan has announced the resumption of HPV vaccination in 2024 [13].

HPV vaccination coverage varies worldwide but is considered to be suboptimal [14]. There are many types of barriers to vaccine uptake, including socioeconomic and communication-related factors. Barriers can arise from the attitudes and actions of governments, health professionals and organisations, schools and parents, guardians, and adolescents themselves, and the importance of specific barriers varies from country to country. One of the main barriers to vaccination is low awareness, misconceptions, and lack of information [15]. Myths surround the vaccine because of its novelty and association with the reproductive system [16,17].

Healthcare providers play a key role in advising parents about their children's immunisation, as they are considered valid and reliable sources of information. Strong recommendation from healthcare providers can increase vaccine uptake by three to nine times [18]. However, misconceptions and lack of knowledge about HPV among healthcare professionals can significantly hinder vaccine uptake [19]. In addition to knowledge gaps, healthcare providers have identified children's age, time constraints, cost, and insurance coverage as significant barriers to recommending HPV vaccination [20,21].

Given the high incidence and prevalence of HPV infection and cervical cancer in Kazakhstan, and the critical role of health professionals, the overall aim of this study was to identify barriers to and facilitators of HPV vaccine uptake in the health sector.

Specific objectives were to assess the level of knowledge about HPV and the HPV vaccine and the intention to recommend the HPV vaccine, in order to draw conclusions on the existing barriers to the introduction and implementation of HPV vaccination among health professionals in the Republic of Kazakhstan.

2. Materials and Methods

This study was part of a larger project investigating attitudes to HPV vaccination among different populations, including parents and guardians, health professionals, and teachers. The full study protocol has been published elsewhere [22]. The present sub-study was conducted from December 2022 to May 2023 in different regions of the Republic of Kazakhstan as a survey among practicing health professionals with secondary (nurses) and higher (physicians) education and different specialisations, using a validated online questionnaire. In Kazakhstan, nurses have various specialisations, including general nursing, midwifery, emergency, pharmacy and dental nursing, massage therapy, and others. Similar to physicians, they are categorized according to their respective specialty. The link to the survey was distributed to professional communities through instant messengers and social networks, as well as to medical organisations through local state authorities.

2.1. Tools and Measurements

The questionnaire designed for health professionals included common general and specific sections. The common questionnaire for all target groups (parents/guardians, health professionals, and teachers) included questions on sociodemographic characteristics such as age, place of residence, gender, and income. The specific section for health professionals included questions on professional characteristics (work experience, place of employment, specialisation), knowledge about HPV and HPV vaccination, and willingness to recommend the HPV vaccine. There were a total of 18 knowledge questions, presented in detail in the study protocol [22], which were scored as follows: correct answers or existing knowledge scored 1 point, and incorrect answers or "I don't know" scored 0. One of the survey questions asked, "How many doses of the HPV vaccine are needed for girls under 15 years of age?" Initially, three doses were recommended, but the WHO later revised this to two, and in 2022, the WHO Strategic Advisory Group of Experts on Immunization endorsed a single-dose option to increase global coverage. In our questionnaire, both 1 and 2 doses were accepted as correct answers [23]. Thus, the maximum score for all answers was 18 points. The questionnaire also included questions to assess the time since knowledge of HPV and HPV vaccination had increased, and where this knowledge had been acquired. Questions were also asked about whether health professionals recommended the HPV vaccine, and about their attitudes towards the COVID-19 vaccine and towards vaccines included in the national vaccination schedule.

The sample size for the study was calculated using the following formula

$$n = 100 + 50i,$$

where i is the number of independent variables in the final logistic regression model [24]. The number of independent variables in our model is 14, so the sample size according to this formula is 800 people.

2.2. Statistical Analysis

All statistical analyses were performed using SPSS 24.0 software (IBM Corp., New York, NY, USA). Descriptive analyses were used to describe sociodemographic variables, knowledge, intentions, and barriers to HPV vaccination, and data regarding HPV vaccination communication. Normality tests showed that the total knowledge scores were not normally distributed, so the Mann–Whitney U test and the Kruskal–Wallis test were used to compare the median and interquartile range (IQR) of knowledge scores across groups. Pearson's chi-squared test was used to compare the proportion of correct answers and sources of information between participants within the 'nurses vs. physicians' and

'low knowledge vs. high knowledge' groups. Low-knowledge health professionals were defined as those who scored less than 11 on all knowledge assessment questions, whereas high-knowledge health professionals were defined as those who scored 11 or more. Binary logistic regression was used to assess the association between independent sociodemographic and professional correlates and the dependent variables of health professionals' knowledge of HPV and the HPV vaccine and intention to recommend HPV vaccination. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, and a *p*-value < 0.05 was considered statistically significant. This study was approved by the Ethics Committee of the Kazakhstan's Medical University "KSPH" (No. 138 of 31 May 2021).

3. Results

3.1. Sociodemographic Characteristics and Knowledge Scores for HPV and HPV Vaccination

A total of 1230 responses were received, of which 40 were excluded because they did not meet the inclusion criteria (37 did not work as health professionals, 3 did not meet citizenship requirements). This left 1189 responses from health professionals, both physicians and nurses, for analysis. The median age of the respondents was 37.0 years (IQR28.0–48.0). The detailed characteristics of the respondents, including their professional characteristics, are shown in Table 1, as are the median scores for knowledge of HPV and the HPV vaccine in the groups.

Table 1. Sociodemographic data of study participants and HPV total knowledge score (median, IQR) (n = 1189).

Characteristics	n	%	Total Score, Me [Q1–Q3]	*p*-Value *
Age (Median, IQR)	37.0 [28.0–48.0]			
Gender				
Female	1045	87.9	11.0 [7.0–14.0]	0.234
Male	144	12.1	10.0 [7.0–14.0]	
Place of residence				
Rural	475	39.9	10.0 [6.0–12.0]	<0.001
Urban	714	60.1	11.0 [8.0–14.0]	
Occupation				
Nurses	591	49.7	9.0 [5.0–11.0]	<0.001
Physicians	598	51.3	13.0 [10.0–15.0]	
Work experience, years				
0–4	316	26.6	9.0 [5.0–13.0]	<0.001
5–10	230	19.3	11.0 [7.0–14.0]	
10–20	298	25.1	12.0 [9.0–14.0]	
More than 20 years	345	29	11.0 [8.0–14.0]	
Medical organization type				
Primary medicine organisation	799	67.2	11.0 [8.0–14.0]	<0.001
Inpatient medical organisation	390	32.8	10.0 [6.0–13.0]	
Specialty				
General practice	201	16.9	10.0 [6.0–13.0]	<0.001
Obstetrics and gynaecology	194	16.3	14.0 [11.0–16.0]	
Other specialties	794	66.8	10.0 [6.5–13.0]	

Table 1. *Cont.*

Characteristics	n	%	Total Score, Me [Q1–Q3]	*p*-Value *
Would you recommend HPV vaccination to your patients?				
No	326	27.4	8.0 [4.0–11.0]	<0.001
Yes	863	72.6	12.0 [8.5–14.0]	
Total knowledge score, median [IQR]	11.0 [7.0–14.0]			

* Mann–Whitney U test and Kruskal–Wallis test were applied.

3.2. Knowledge of HPV and HPV Vaccine Among Healthcare Professionals

The median score for knowledge of HPV and the HPV vaccine among healthcare professionals in Kazakhstan was 11.0 [7.0–14.0] points (median, IQR) out of a maximum of 18 points. A high level of knowledge (defined as a percentage of correct responses of over 80%) was demonstrated by 17.1% of healthcare professionals. Physicians had significantly higher knowledge scores than nurses (13.0 vs. 9.0, *p* < 0.001), and primary care workers outperformed hospital staff (11.0 vs. 10.0, *p* < 0.001). Healthcare professionals specialising in obstetrics and gynaecology had the highest knowledge (14.0), followed by those specialised in general practice and other specialties (10.0) (*p* < 0.001). Knowledge increased with experience, and urban respondents scored higher than rural respondents (11.0 vs. 10.0, *p* < 0.001). A strong association was found between higher knowledge and the intention to recommend HPV vaccination, indicating that better informed professionals are more likely to support vaccination (Table 1).

The distribution of correct answers was compared between nurses and physicians (Figure 1), and between healthcare professionals specialising in obstetrics and gynaecology and other specialties (Supplementary Table S1). On average, nurses demonstrated a percentage of correct answers of 44.1%, and physicians demonstrated a percentage of 66.5%. Healthcare professionals specialising in obstetrics and gynaecology showed the best knowledge, with an average percentage of correct answers to all questions of 70.9%, compared with 52.4% for other specialties. The most difficult questions for all groups were specific questions about types of HPV associated with cancer, prevention of HPV infection, primary prevention of CC, and routes of HPV transmission.
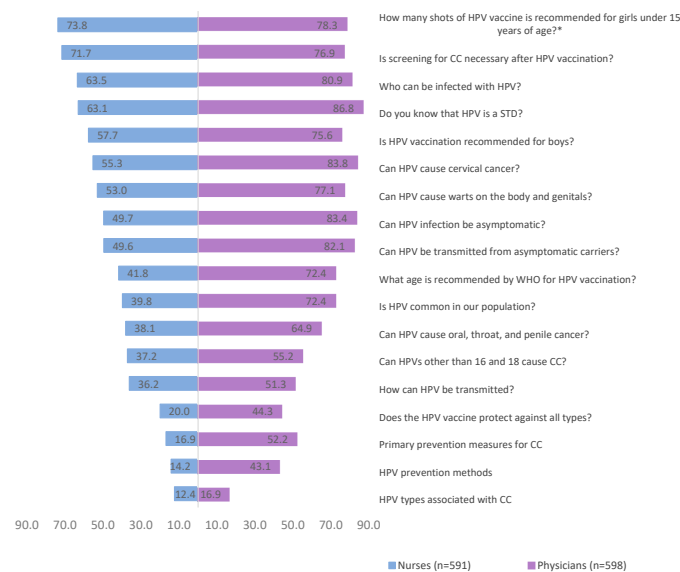

Figure 1. Comparison of correct answers between nurses and physicians, % (from Supplementary Table S2). * *p* > 0.05.

3.3. Factors Influencing Healthcare Professionals' Knowledge of HPV and Vaccine Recommendation

Almost three-quarters of survey participants (72.6%) expressed a positive intention to recommend HPV vaccine to their patients.

Table 2 shows the multivariate logistic regression analysis models examining the association of higher knowledge and awareness of HPV and the HPV vaccine (≥11 out of 18) among healthcare professionals in Kazakhstan, and their positive intention to recommend the HPV vaccine to patients, with the study covariates. Higher knowledge scores were significantly associated with urban versus rural residence, higher income, higher education, specialisation in obstetrics and gynaecology, and more recent training in HPV knowledge and ongoing professional updates regarding HPV. In addition, higher knowledge scores were associated with positive attitudes towards childhood vaccination and with knowing people with cervical cancer. Factors such as gender, age group, and work experience were not significantly associated with higher knowledge.

Table 2. Multivariate logistic regression analysis assessing factors associated with providers' knowledge of HPV and the HPV vaccine and their recommendation of HPV vaccination (n = 1189).

Variables	Higher Knowledge Score (≥11) OR *; 95%CI	*p*-Value	Positive Intention to Recommend HPV Vaccination OR; 95%CI	*p*-Value
Age groups				
20–29 years old	Reference group		Reference group	
30–39 years old	0.983; 0.619–1.561	0.943	0.843; 0.536–1.325	0.459
40–49 years old	0.902; 0.553–1.471	0.679	0.856; 0.533–1.373	0.518
50–59 years old	0.968; 0.582–1.611	0.901	0.950; 0.572–1.578	0.844
60 and over	1.091; 0.479–2.484	0.835	0.710; 0.324–1.556	0.393
Gender				
Female	Reference		Reference	
Male	0.747; 0.478–1.169	0.202	0.866; 0.567–1.324	0.507
Place of residence				
Rural	Reference		Reference	
Urban	1.599; 1.161–2.201	0.004	0.875; 0.636–1.204	0.412
Monthly personal income				
Less than KZT 147.000 (less than USD 312)	Reference		Reference	
Over KZT 147.000 (over USD 312)	1.445; 1.045–1.999	0.026	0.811; 0.585–1.125	0.209
Education				
Nurses	Reference		Reference	
Physicians	4.484; 3.233–6.217	<0.001	1.111; 0.797–1.550	0.535
Religion				
Muslim	Reference		Reference	

Table 2. *Cont.*

Variables	Higher Knowledge Score (≥11) OR *; 95%CI	*p*-Value	Positive Intention to Recommend HPV Vaccination OR; 95%CI	*p*-Value
Christian	2.038; 1.268–3.275	0.003	0.530; 0.344–0.818	0.004
Other	N/A**		N/A**	
Not religious	4.054; 1.960–8.387	<0.001	0.625; 0.336–1.162	0.137
Level of religiosity				
Not religious	Reference		Reference	
Not really religious	1.582; 0.899–2.783	0.112	1.637; 0.962–2.786	0.069
Moderately religious	2.360; 1.434–3.884	0.001	1.151; 0.729–1.819	0.546
Quite religious	1.864; 1.052–3.302	0.033	1.364; 0.797–2.334	0.257
Very religious	1.357; 0.608–3.028	0.456	1.441; 0.662–3.138	0.358
Work experience. years				
<5 years	Reference		Reference	
≥5 years	1.428; 0.927–2.199	0.106	0.846; 0.554–1.294	0.441
Specialty				
General practice	Reference		Reference	
Obstetrics–gynaecology	4.221; 2.325–7.664	<0.001	0.994; 0.566–1.744	0.982
Other specialties	1.080; 0.729–1.601	0.701	0.588; 0.391–0.885	0.011
Time since last HPV and HPV vaccine knowledge update				
More than 10 years ago	Reference		Reference	
5–10 years ago	0.911; 0.481–1.725	0.775	1.582; 0.888–2.819	0.120
Up to 5 years	2.250; 1.413–3.583	0.001	1.602; 1.057–2.427	0.026
Update constantly	2.682; 1.609–4.471	<0.001	3.202; 1.966–5.213	<0.001
Attitudes to COVID-19 vaccination				
Negative/Doubtful	Reference		Reference	
Positive	1.157; 0.838–1.597	0.377	2.276; 1.674–3.096	<0.001
Children National Vaccination Program attitude				
Negative/Doubtful	Reference		Reference	
Positive	2.695; 1.924–3.773	<0.001	1.462; 1.053–2.030	0.023
HPV and HPV vaccine knowledge				
Lower (total score ≤ 11.0)	N/A**		Reference	

Table 2. *Cont.*

Variables	Higher Knowledge Score (≥11) OR *; 95%CI	*p*-Value	Positive Intention to Recommend HPV Vaccination OR; 95%CI	*p*-Value
Higher (total score > 11.0)	N/A**		1.823; 1.304–2.547	<0.001
Having familiar people with cervical cancer				
No	Reference		Reference	
Yes	2.206; 1.631–2.984	<0.001	2.040; 1.504–2.767	<0.001

* OR; 95%CI—odds ratio with 95% confidence interval. ** N/A: Not Applicable.

A positive intention to recommend the HPV vaccine was significantly higher among those with higher HPV knowledge scores, those who continually updated their HPV knowledge, those familiar with cervical cancer, and those with positive attitudes towards the COVID-19 vaccine and childhood vaccination within the national schedule. Each knowledge point increased the likelihood of recommending the HPV vaccine by 43%. Professionals who constantly update their knowledge of HPV and the vaccine are almost three times more likely to recommend HPV vaccination than those who have not updated their knowledge for more than 10 years. Professionals in specialties other than general practice and obstetrics were less likely to recommend the HPV vaccine. A positive intention to recommend the vaccine was not associated with gender, age, place of residence, work experience, income, religion, or level of religiosity.

3.4. Healthcare Professionals' Perception of Barriers to HPV Vaccine Uptake

As part of the survey of healthcare professionals, barriers to HPV vaccine uptake were investigated. Figure 2 presents data on the prevalence of these barriers among health professionals in Kazakhstan. The most important barrier, according to healthcare professionals, is the general mistrust of citizens towards all vaccines, reported by 49.4% of respondents. This was closely followed by public fear of HPV vaccine side effects, lack of information about the HPV vaccine among parents, and the absence of the HPV vaccine in the national immunisation schedule. At the time of the survey (2023), the HPV vaccine was not yet included in the national immunisation calendar in the Republic of Kazakhstan.
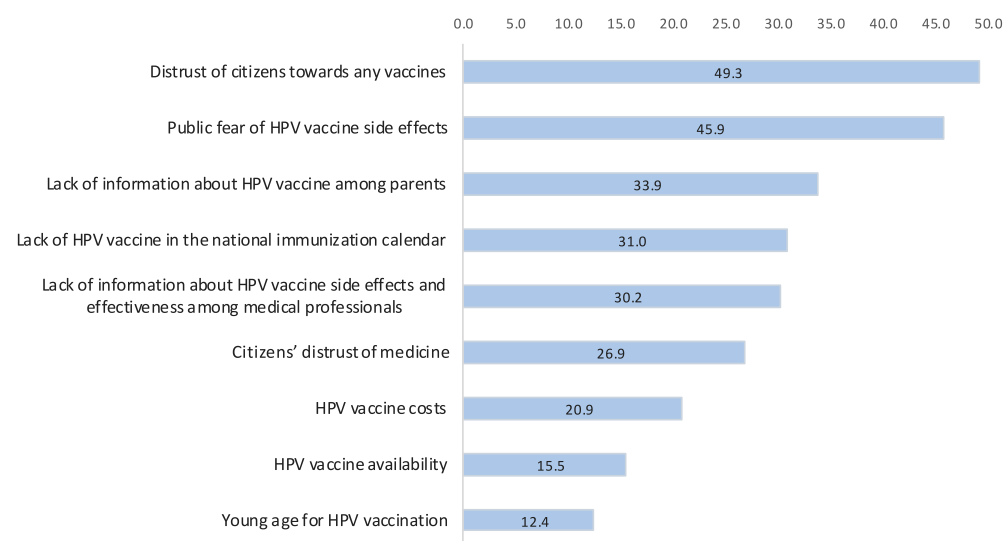
Figure 2. Barriers to HPV vaccination as reported by healthcare professionals in Kazakhstan (n = 1189), %.

More than half of respondents (52.0%) reported difficulties in advising patients about HPV vaccination. Lack of information about the HPV vaccine, its safety profile, and effectiveness were the most common reasons for these difficulties. The unavailability of the vaccine was cited by 8.6% of healthcare professionals, and discomfort about discussing children's sexual behaviour was cited by 5.8%.

3.5. HPV Vaccination Information Channels and Communication Practices Among Healthcare Professionals

Among survey participants, 90.0% of healthcare professionals expressed a strong desire to improve their knowledge of HPV and the HPV vaccine, with 20.5% reporting that their last knowledge update was more than five years ago. Almost half cited internet journals and articles as their primary source of information, followed by professional groups on social media and online forums, and input from colleagues. Figure 3 illustrates the prevalence of various sources used for knowledge acquisition and updating among healthcare professionals in Kazakhstan.
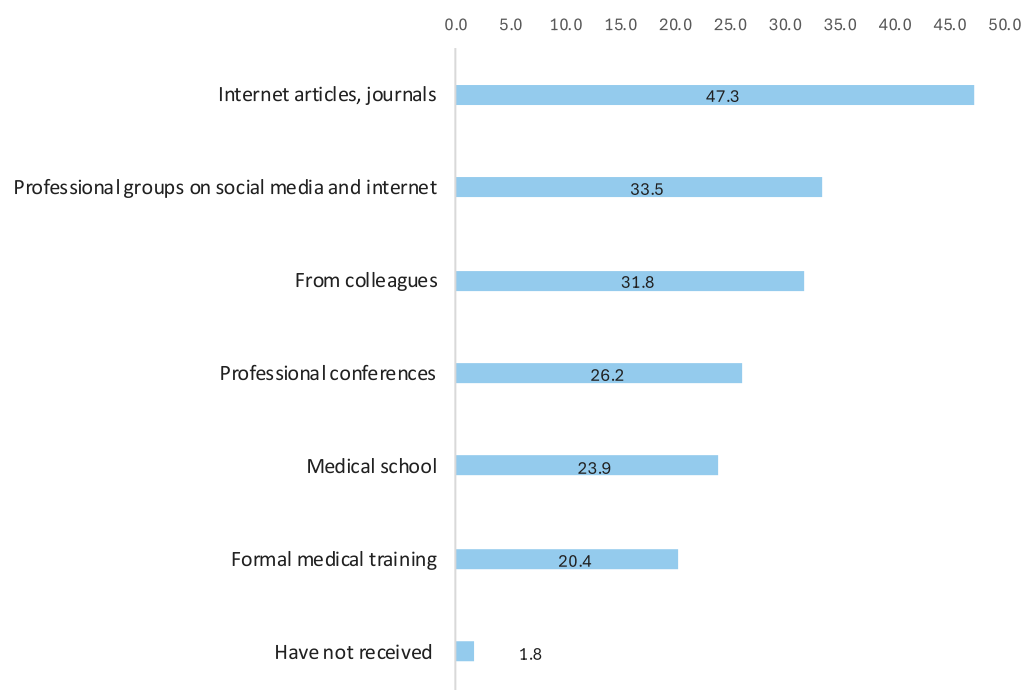
Figure 3. Sources used for acquiring and updating knowledge of HPV and HPV vaccines among healthcare professionals in Kazakhstan (n = 1189), %.

Differences in sources of information about HPV and the HPV vaccine were observed between nurses and physicians and between allied health professionals with lower (<11.0) and higher (≥11.0) knowledge in Kazakhstan (Table 3 and Supplementary Table S3). The most commonly used sources of knowledge among nurses were internet journals and articles, followed by colleagues and social media. In contrast, physicians mainly relied on internet journals and articles, followed by social media, medical school, and professional conferences. Physicians generally used a wider range of academic and professional sources than nurses. Among those who received no information about HPV and the HPV vaccine, the proportion of nurses was more than double that of physicians (2.7% vs. 0.8%; *p* = 0.015).

An analysis of sources of information among healthcare professionals with lower (<11.0) and higher (≥11.0) HPV knowledge scores showed that those with higher scores were more likely to have received information from medical school (28.7% vs. 17.6%), formal training (26.2% vs. 12.8%), internet journals (55.8% vs. 36.2%), conferences (36.0% vs. 13.5%), and professional social media groups (42.1% vs. 22.2%) (Supplementary Table S3).

Table 3. Comparative analysis of sources of information about HPV and HPV vaccine used by nurses and physicians in Kazakhstan (n = 1189).

	Nurses (n = 591)		Physicians (n = 598)		Test of Difference	*p*-Value
Information source	n	%	n	%	χ^2	
Internet articles, journals	231	39.1	331	55.4	31.55	<0.001
Colleagues	202	34.2	176	29.4	3.09	0.081
Professional groups on social media	164	27.7	234	39.1	17.29	<0.001
Formal medical training	106	17.9	136	22.7	4.24	0.044
Professional conferences	97	16.4	215	36.0	58.64	<0.001
Medical school	68	11.5	216	36.1	99.06	<0.001
Have not received	16	2.7	5	0.8	6.0	0.015
Other	3	0.5	1	0.2	1.03	0.371

4. Discussion

Over the past 15 years, there has been an increase in the incidence of CC among Kazakhstani women, with the peak incidence shifting to a younger age group, from 50–55 years to 40–44 years [25]. Since 2008, Kazakhstan has implemented a national cytology-based screening programme for CC, with coverage rates varying from 46.2% in 2012 to 83.2% in 2019. Consequently, there has been a modest decline in mortality rates [26,27]. However, challenges remain, particularly with regard to HPV-based screening and vaccinating younger populations against HPV. Studies indicate that transitioning to HPV-based screening enhances programme effectiveness, while the introduction of self-testing improves access to screening, particularly for women in underserved areas, and could raise awareness about HPV [28,29]. The HPV vaccination programme in Kazakhstan was suspended four years after its introduction due to widespread parental refusal, spurred by extensive media coverage of side effects. Possible reasons for this refusal included low awareness and poor communication from health services to parents and adolescents, coupled with the dissemination of negative information in the media [12]. As is known based on a similar situation in Japan [30], this probably will increase the future burden of CC among girls born between 2005 and 2012 in Kazakhstan due to missed immunisation. In this study, we analysed the level of knowledge about HPV and the HPV vaccine, the desire to recommend the HPV vaccine, and perceived barriers to the introduction and implementation of HPV vaccination among healthcare professionals in the Republic of Kazakhstan. In particular, we analysed associations with demographic, social, and professional determinants.

4.1. Knowledge of HPV and the HPV Vaccine

In this survey, participants answered an average of 61.1% of questions about HPV and the HPV vaccine correctly, with the largest gaps being in specific advanced knowledge. Higher levels of knowledge were found among healthcare professionals with higher education and income, in urban areas, with more professional experience, from primary healthcare organisations, specialising in obstetrics and gynaecology, and those who had updated their HPV knowledge within the last five years.

Several studies have shown that knowledge levels vary by specialty, gender, work setting, working hours, and recent HPV education [31,32]. General practitioners, gynaecologists, and paediatricians showed higher awareness of HPV genotypes than other specialties, with knowledge differences observed between rural and urban practitioners [33]. In other studies, lower levels of knowledge were associated with male gender, fewer hours worked

in a clinic, and smaller health centres [34]. A study of knowledge among health professionals in the United Kingdom found that more recent training correlated with higher levels of knowledge [35].

The main knowledge gaps in our study were in more advanced knowledge (oncogenic HPV genotypes, vaccination of boys, dosage regimen), while relatively general questions did not pose difficulties. Similarly, in all countries, up to 60–80% of professionals had a high level of knowledge about HPV infection, but lacked a detailed understanding of vaccine mechanisms and the benefits of HPV vaccination [31].

4.2. Intention to Recommend HPV Vaccination

In our study, 72.6% of health professionals were willing to recommend HPV vaccination for girls. This is consistent with other studies, where the average intention to recommend HPV vaccination was 66.9%. In these studies, increased rates of HPV vaccine recommendation were associated with higher levels of knowledge, national and professional guidelines on HPV vaccination, and beliefs in the efficacy and safety of the vaccine [32]. In our study, physicians with higher knowledge of HPV and the HPV vaccine, those specialising in obstetrics and gynaecology and general practice, and those with a positive attitude towards the COVID-19 vaccine were statistically significantly more likely to recommend HPV vaccination. However, this association was not observed in all groups; for example, specialists with two or more university degrees had higher knowledge but were less likely to recommend the vaccine. Some studies also suggest that knowledge of HPV and the HPV vaccine does not always lead to recommendation. Chawla et al. found that only 47% of participants would recommend HPV vaccination to young women, although 81% were aware of vaccines to prevent CC [33]. One explanation for low vaccination uptake may be a strong awareness of other methods of preventing cervical cancer, such as Pap smears [36]. However, most studies suggest that lack of information and knowledge about HPV and CC among health professionals is the main reason for low uptake of HPV vaccination programmes, especially among nurses [31].

In our study, physicians were more likely to recommend HPV vaccination than nurses. This is consistent with a study of COVID-19 vaccination, where nurses were significantly more likely to refuse vaccination [37]. In our survey, specialists were more likely than others involved in HPV vaccination (general practitioners, family physicians, and obstetricians/gynaecologists) to have a higher intention to recommend HPV vaccination, which may be a positive sign for a successful HPV vaccination programme. Factors such as gender, income level, level of religiosity, and work experience did not have a statistically significant association with intention to recommend HPV vaccination among health professionals in Kazakhstan.

4.3. Barriers to Recommending HPV Vaccination

In our study, health professionals identified several barriers to HPV vaccination in Kazakhstan, including citizens' mistrust of all vaccines and fear of side effects. A significant number of participants cited a lack of information about the side effects and effectiveness of the HPV vaccine as a barrier to recommending it. In our study, mistrust of medicine was identified as a significant barrier to HPV vaccination, consistent with another study [38]. Participants identified low parental awareness of the HPV vaccine as a common barrier, similar to findings in the United States, where low parental education was identified as a barrier [39]. Trust in health professionals and strong recommendations from physicians are important factors in parents' decisions to vaccinate their children against HPV [40].

Parental fear of side effects was another common barrier to HPV vaccination identified by health professionals. The HPV vaccine, no less than other types of vaccines, is surrounded by many misconceptions and fears, especially regarding its safety [16,41]. HPV vaccination in Kazakhstan was directly affected by these misconceptions, which ultimately led to the failure of the pilot programme in 2017 [12]. The challenge for health professionals is to address these misconceptions. Research during active vaccination against COVID-19

shows an increased prevalence of burnout among healthcare workers involved in vaccination, highlighting the need for psychological support [42]. In our study, about half of the health workers experienced difficulties in counselling about the HPV vaccine, often due to lack of information and less often due to its inaccessibility and concerns about its association with children's sexual behaviour. A study of Ghanaian nurses found that the majority of unvaccinated participants cited lack of information about HPV vaccination as a factor in their decision [43]. Most participants in our study expressed a desire to improve their knowledge of the HPV vaccine, highlighting the need for increased education and awareness among healthcare professionals in Kazakhstan.

4.4. Communication and Sources of Information

Our study showed differences in information sources for acquiring and updating knowledge about HPV and the HPV vaccine between nurses and physicians, and between health professionals with different levels of knowledge. In our study, physicians and health professionals with higher levels of knowledge about HPV and the HPV vaccine appeared to use a wider range of information sources and to rely more on academic and professional channels than nurses and health professionals with lower levels of knowledge. Regardless of the group, a significant number of healthcare professionals actively engaged in professional communication with each other, including through social media platforms. Analysis of the sources of knowledge updates among healthcare professionals reveals a strong reliance on scientific literature and educational programmes offered by universities and other educational institutions. In addition, health professionals actively engage in professional communication through conferences and professional groups on social networks. In our study, formal professional education in medical schools and training programmes were cited as sources of information by 36.1% and 22.7% of physicians, respectively. In comparison, a higher proportion of physicians in the United States reported receiving information from professional organisations (50.0%) and the Advisory Council on Immunization Practices (36.0%). A similar proportion of physicians in both Kazakhstan and the United States reported using conferences as a source of information (36.0% and 33.1%, respectively). Consultation with colleagues was also a common source in both countries, with 29.4% of Kazakh physicians and 32.4% of American physicians relying on this method, which may reflect similarities in information-seeking behaviour. In contrast, the use of internet sites as a source of information was significantly higher in Kazakhstan (55.4%) than in the United States, where only 20.2% of obstetricians and gynaecologists reported using online resources. This difference may be due to the limited information available from professional organisations in Kazakhstan [44]. A study from Norway found that public health nurses were more likely to obtain knowledge from the Norwegian Institute of Public Health, while general practitioners were more likely to rely on professional journals and reference books. However, in our study, nurses were significantly less likely to use training programmes, because the HPV vaccination campaign had not yet started at the time of the study [45]. Globally, consultation with colleagues, reading journal articles, and using online resources such as Medline/PubMed are among the most commonly used methods by physicians for obtaining information. However, factors such as lack of time and inadequate search skills are commonly cited as barriers to accessing the information they need [46]. Mistrust of vaccination and medicine among citizens was one of the main barriers identified by healthcare professionals in our study, highlighting the need for communication training for healthcare workers on how to talk to vaccine-hesitant individuals. Studies show that regular training in communication, combined with other strategies, can effectively increase vaccination coverage [39,47]. Moreover, studies indicate that when physicians talk about HPV vaccination, their messages are often perceived as condescending, highlighting the need for specialised training in effective public communication [48].

Limitations

This study is the first in Kazakhstan to investigate the knowledge, awareness, and attitudes of health professionals regarding HPV and the HPV vaccine. However, several limitations must be acknowledged. This study was conducted at a time when the HPV vaccine was not available or introduced in the country. Therefore, knowledge and opinions may change as vaccination practices become more established. The use of a questionnaire and snowball sampling may have affected the representativeness of the sample. The involvement of medical organisations in the distribution of the questionnaires was intended to mitigate this limitation. In our study, the majority of healthcare professionals were female and urban residents, which may influence the representativeness of the sample due to the sampling method. However, the Bureau of Statistics of Kazakhstan reports an urban-to-rural population ratio of 1.7:1, and women account for 70–80% of healthcare workers in the country. While internet access is generally widespread in Kazakhstan, some areas still lack adequate access or face financial barriers, which may have excluded some participants. In our study, the survey was distributed via Google Forms across multiple digital platforms, including social media and email. The use of this online survey method made it impossible to determine the survey response rate, as the total number of individuals who received the survey link is unknown. Acknowledging this limitation, we selected this method to ensure broader reach. The study design does not allow causal relationships to be established between influencing factors and intention to recommend the HPV vaccine. In addition, the mix of simple and complex questions in the questionnaire may have influenced the overall responses, potentially biasing the results.

5. Conclusions

This study found that knowledge of HPV and the HPV vaccine among health professionals in Kazakhstan varied significantly by specialty, educational background, and other sociodemographic and professional characteristics. Higher levels of knowledge were associated with an increased likelihood of recommending HPV vaccination. These findings highlight the urgent need for a tailored, multifaceted communication strategy that addresses the diverse needs of health professionals in Kazakhstan, including by reducing inequalities in knowledge acquisition and increasing access to quality knowledge through medical education and continuing education opportunities for nurses, especially those involved in the vaccination process. Educational programmes for health professionals should include both medical school and specialised training to improve knowledge of HPV and the HPV vaccine. International public health organizations including WHO, UNICEF, GAVI, and others, provide essential support to healthcare professionals by offering resources, training, and public outreach. This collaboration enhances countries' capacity to strengthen HPV prevention efforts and improve vaccination coverage, particularly in resource-limited settings. Access to reliable information should also be widened through the organisation of conferences, improved access to journals in the language most easily understood, and the development of professional websites with high-quality information on the HPV vaccine. The widespread use of social networks, as well as peer-to-peer communication among health professionals to gain knowledge, demonstrates the need to encourage experts to disseminate accurate information and facilitate discussions on these platforms about the upcoming introduction of HPV vaccination. A comprehensive approach should also include specialised training, not only to increase knowledge of HPV and the vaccine, but also to communicate with parents/guardians and adolescents. Future research should evaluate the effectiveness of these methods, while adapting evidence-based international practices to local conditions to improve the success of the HPV vaccination programme in Kazakhstan.

The results of this study can help inform the public health strategies and policies of the Republic of Kazakhstan, contribute to the development of educational and policy initiatives with targeted communication to prevent a repetition of previous negative experiences with HPV vaccination in Kazakhstan, more fully prepare and aid the development of a country-specific communication plan for the upcoming introduction of the HPV vaccine,

and contribute to local and global efforts to eliminate cervical cancer and other HPV-associated diseases. In addition, improving communication strategies with the public to increase confidence in medical and preventive measures remains a major public health challenge. This requires taking into account local social and cultural characteristics to improve the uptake and implementation of vaccination programmes.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/vaccines12111225/s1, Table S1: Distribution of correct answers on questions about HPV and HPV vaccine between healthcare professionals of Non- Obstetrician -Gynecologist and Obstetrician -Gynecologist specialty; Table S2: Distribution of right answers on questions about HPV and HPV vaccine between healthcare professionals of Nurses and Physicians; Table S3: Comparison of sources of information about HPV and HPV vaccine among healthcare professionals with low (<11.0) and high (≥11.0) knowledge (n = 1189).

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Institutional Review Board Statement: The study protocol was approved by the Ethics Committee of the Kazakhstan's Medical University "KSPH" (No: 138 of 31 May 2021). All methods were carried out in compliance with relevant guidelines and regulations.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets used and analysed in the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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BMJ Open

Exploring HPV vaccine knowledge, attitudes, barriers and information sources among parents, health professionals and teachers in Kazakhstan: a mixed-methods study protocol

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ABSTRACT

Introduction Human papillomavirus (HPV) is a prevalent sexually transmitted infection linked to certain types of malignant neoplasms, notably cervical cancer (CC). In Kazakhstan, a high prevalence of high oncogenic HPV types (HR-HPV) has been observed, and CC ranks as the second most common malignancy among women with a crude incidence rate of 18.3 cases per 100 000 women. The HPV vaccine, developed as the primary prevention measure against HPV infection, including the most prevalent HR-HPV, received approval from the WHO in 2009. In 2014, Kazakhstan initiated HPV vaccination as a pilot project in four sub-national regions; however, it was later in 2017 discontinued due to widespread parental refusal influenced by negative media reports. This study aims to examine knowledge, attitudes, information sources, barriers to HPV vaccination and factors associated with HPV vaccination hesitancy among different target groups in Kazakhstan prior to the HPV vaccine re-launch announced by the Ministry of Health.

Methods and analysis This mixed-method-designed research comprises quantitative and qualitative components. Data on HPV awareness, attitudes towards HPV vaccination and sources of information will be collected through an online survey administered by parents and legal guardians, health professionals, and schoolteachers in the Republic of Kazakhstan between January 2023 and January 2024. Additionally, qualitative data on Kazakhstani parental beliefs and attitudes toward HPV vaccination will be collected through online focus group discussions.

Ethics and dissemination of results The study has been approved by the local ethics committee at the Kazakhstan Medical University "Higher School of Public Health" (KMU "KSPH") (No. 138 of 31.05.2021). The results will be reported in publications, at conferences among researchers and healthcare and school education professionals in Kazakhstan, and internationally.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is the first of its kind to examine human papillomavirus vaccination related knowledge, attitudes, barriers and information sources in Kazakhstan.
⇒ The study covers rural and urban areas and addresses multiple target groups.
⇒ By using a mixed-method design, the study allows for a more extensive evaluation.
⇒ Non-probabilistic sampling in online surveys may lead to a biased study sample.

INTRODUCTION

Human papillomavirus (HPV) is one of the most common sexually transmitted infections. The persistence of high-risk HPV types (HR-HPV) increases the risk of developing cervical, oropharyngeal, oral, laryngeal, anal, penile, vaginal and vulvar cancers.[1] Studies show that 5.2% of all cancers and 16% of gyneacological cancers worldwide are linked to HPV, with an average incidence of 8.0 per 100 000 person-years. Moreover, HPV causes benign diseases such as genital and oropharyngeal warts in adults and children, significantly affecting quality of life and increasing costs for patients and the healthcare system. Up to 80% of all HPV-associated cancers are cervical cancers (CC).[2 3] CC is the fourth most common cancer in women worldwide, causing more than 300 000 deaths per year. New cases of CC are more common in low-income and middle-income countries, where early diagnosis and prevention programmes are limited. In the Republic of Kazakhstan the prevalence HR-HPV infection is substantial and ranges from 43.8% to 55.8%.[4] Among

women attending outpatient clinics with normal and abnormal cytological results, the prevalence of HR-HPV reaches 39%, with the most common types being HPV 16 (54%), followed by HPV 51, 68 and 18.[5] In addition to HPV 16 and 18 types, the prevalence of other HR-HPV types among women is also high, reaching up to 22%.[6] Since 2008, Kazakhstan has implemented a national population-based CC screening programme, targeting specific age groups and intervals adjusted over time. The programme currently targets women aged 30–70 years and screens once every 4 years. This screening protocol involves the collection of either liquid-based or conventional cytological samples using the Papanicolaou method for examination. The interpretation of results follows the Bethesda Terminology System (2001), and if necessary, colposcopy and/or cervical biopsy are conducted for further evaluation and treatment.[7 8] Despite the continuous efforts, CC remains a significant public health concern and the second most prevalent malignancy among Kazakhstani women, accounting for approximately 1800 incident cases and 600 deaths annually.[9 10] In 2021 in Kazakhstan, CC exhibited a crude incidence rate of 18.3 cases per 100 000 women and a crude mortality rate of 9.1 per 100 000 women.[11] Over the period from 2009 to 2018, there was a trend of increase in the overall incidence of CC in the Republic of Kazakhstan, as well as in all its regions.[12]

In 2006, with the introduction of the first HPV vaccine, primary prevention of HR-HPV-associated diseases became available.[13] Even though by 2021, 120 (61%) of the 194 WHO member states had introduced HPV vaccination, about 70% of the world's female population is not covered.[14] The safety and efficacy of the HPV vaccine have been repeatedly proven in numerous studies. The effectiveness of the vaccine against HPV infection reaches 93%–97%, and in the prevention of both intraepithelial neoplasia and CC its effectiveness is up to 98.7% and 86%, respectively.[15–18]

HPV vaccination coverage varies globally but is considered suboptimal.[19] There are many types of vaccine uptake barriers, which can be divided into infrastructural, socioeconomic and communication-related factors. Barriers can exist on the part of the state, medical professionals and organisations, schools and parents, legal guardians and adolescents themselves, while the significance of certain barriers may vary from country to country.

Patients' main barriers to vaccination include low awareness, misconceptions and lack of information.[20] The vaccine is surrounded by myths due to its novelty and reproductive system link.[21 22] To address these myths, educational training of healthcare professionals and stakeholders is essential.[23] Meanwhile, knowledge gaps about HPV vaccination among healthcare professionals in various countries have a significant impact on vaccine uptake, leading to challenges during counselling, including those related to sexual issues.[24 25] Additional medical specialists' barriers, such as children's age, time constraints, cost and insurance coverage hinder HPV

vaccination.[26 27] Strong advice from healthcare professionals plays a significant role for parents in the decision to vaccinate, which can increase vaccination rates by three to nine times.[24]

Most countries (61.3%) choose schools as the primary vaccination site in order to achieve greater coverage that require an active role of schoolteachers in the vaccination process.[28] Teachers' better knowledge leads to stronger recommendations to parents and students.[29] The source of information related to HPV vaccination and its credibility play an important role in the degree of HPV vaccine awareness. People get their information from medical resources, friends and family members, the media, social networks, radio, etc, while the prevalence, reliability and credibility of different sources may differ from country to country and within societies.[30] In terms of reliability, the media and medical doctors are considered the most dependable sources, whereas information obtained from friends is associated with lower levels.[31] In Kazakhstan, HPV vaccination was initiated as a pilot project in four sub-national regions in 2014 but was discontinued in 2017 due to widespread media reports about potential/perceived side effects of the vaccination followed by mass parental refusal.[32] However, the Ministry of Health of Kazakhstan has announced plans to re-introduce HPV vaccination in the coming years.[33] Previous studies among women in Kazakhstan have indicated a low level of awareness about HPV and HPV vaccination, with only slightly over half of them displaying a positive attitude towards the vaccine.[34] There is a research gap regarding the knowledge of attitudes towards HPV vaccination among parents and caregivers, barriers to recommending HPV vaccination by physicians and teachers, and the specifics of communication in Kazakhstan. This study aims to explore the level of preparedness for HPV vaccination in Kazakhstan by examining knowledge, attitudes, information sources, barriers to HPV vaccination, and factors influencing HPV vaccination hesitancy and recommendation among different stakeholders involved in vaccination, including parents, schoolteachers and health professionals. The results will be useful for creating a communication plan for the initiation and continuation of the HPV vaccination programme in Kazakhstan.

RESEARCH OBJECTIVES AND HYPOTHESES
The main objectives of this study are:
1. To explore the level of awareness and knowledge about HPV and the HPV vaccine among parents and legal guardians, healthcare professionals and school professionals in the Republic of Kazakhstan.
2. To assess the prevalence of parental hesitancy towards HPV vaccination and to assess its correlation with knowledge, awareness about HPV and HPV vaccination, sources of information and sociodemographic factors. As a hypothesis, we assume that higher levels of knowledge and more reliable sources of informa-

tion are associated with a higher intention to vaccinate children.

3. To identify parental existing and preferred sources, channels and methods of communication for obtaining information about HPV and HPV vaccination.
4. To examine barriers by healthcare professionals and schoolteachers to HPV vaccination and their willingness to recommend it.
5. To understand attitudes toward the introduction of the new HPV vaccine among parents and legal guardians by assessing barriers and motivating factors in group discussions.

Given the past negative experience of HPV vaccination in Kazakhstan, we assume low levels of awareness and high prevalence of myths and misconceptions about the HPV vaccine in the different target groups of this study. Confirmation of this fact will provide a clear understanding of the necessary content of educational interventions and information campaigns for all stakeholder groups, including parents, schoolteachers, healthcare professionals and others. Therefore, this research will be relevant in identifying potential challenges decision-makers may encounter and will help to prepare for tailored communication strategies.

METHODS AND ANALYSIS
Study design
A mixed-method research design will be used, combining sequentially quantitative and qualitative research methods.

Survey methodology
The quantitative part of this study comprises three types of cross-sectional surveys among parents and legal guardians of boys and girls under 18 years old, teachers and health professionals (figure 1).

Interviews will be conducted through electronic self-administered, anonymous basic questionnaires dedicated to all three groups, with specialised questions for health professional and schoolteachers. Convenience sampling with snowballing will be done by disseminating invitation links to an online questionnaire created in Google Forms. This link will be sent out two or three times each to parent communities, school chats, professional communities in messengers and social networks. Health professionals and teachers will also be recruited by mailing to schools and medical clinics through local state government offices. In addition, QR codes to the survey will be posted in medical clinics and schools across the country to better reflect the heterogeneity of the country and cover different regions with different social structures (32 medical organisations and 17 schools in Almaty, Astana, Shymkent, Aktau, Kokshetau, Kyzylorda, and villages of Almaty, North Kazakhstan, East Kazakhstan, and Kyzylorda regions). Organisations could take part in the study through consent of their head. Data collection will occur during 2023–2024 (January 2023 to January 2024) (figure 2).

Qualitative part of the research
The second stage of studying parental barriers, beliefs and attitudes toward HPV vaccination is conceived as 1-hour online focus group discussions with recording. The quantitative questionnaire for parents will include a question about the willingness to participate in a focus group discussion, with an option to indicate contact details. Subsequent selection for focus groups will be random among those who wish to participate. During group discussion, reflection and expression of new ideas are formed, while leading the line of discussion within the topic. In the beginning, the group has no structure in terms of certain roles of the participants; however, we assume that while the opinions of all participants are expressed, leaders are formed around whom the micro-group gathers. Researchers observe which issues resonate the most and how group and public opinion is formed. A moderator (principal investigator) and an assistant will guide the focus group discussions.

Objects of research and sample size calculation
The study design targeting three population sub-groups in quantitative part and parents and legal guardians of girls and boys under 18 years of age in focus groups. The selected study participants were determined considering the WHO recommendations on HPV vaccination age (girls 9–14 years old and catch-up vaccination up to 18 years old). As children and adolescents at this age cannot receive any healthcare without parental or legal guardian consent, this category is included in the study.[35]

Inclusion and exclusion criteria
Inclusion criteria for the three surveys were (1) a citizen of the Republic of Kazakhstan who is (2) a parent or legal guardian of children of both genders under 18 years old or (3) an employed health professional nurse or doctor of any specialisation or (4) an employed schoolteacher and (5) willing to participate (table 1). In Kazakhstan, elementary schools teach children from ages 6–7 to 9–10; therefore, it was decided to include all schoolteachers in the study without dividing them into primary and secondary schools. The inclusion criteria for focus groups were Kazakhstani parents or legal guardians of girls and boys under 18 years old gave their consent to participate in the course of the quantitative parental survey.

Sample size
Sample size calculations for surveys
The sample size for the parent survey was determined by the formula recommended for multivariate regression: $n=100+50i$, where i refers to the number of independent variables in the final model (the number of independent variables in the model is −15, and the sample size according to this formula is 850 participants).[36] According to the same formula, the total sample of medical professionals will be at least 270 participants and for teachers 225 participants.
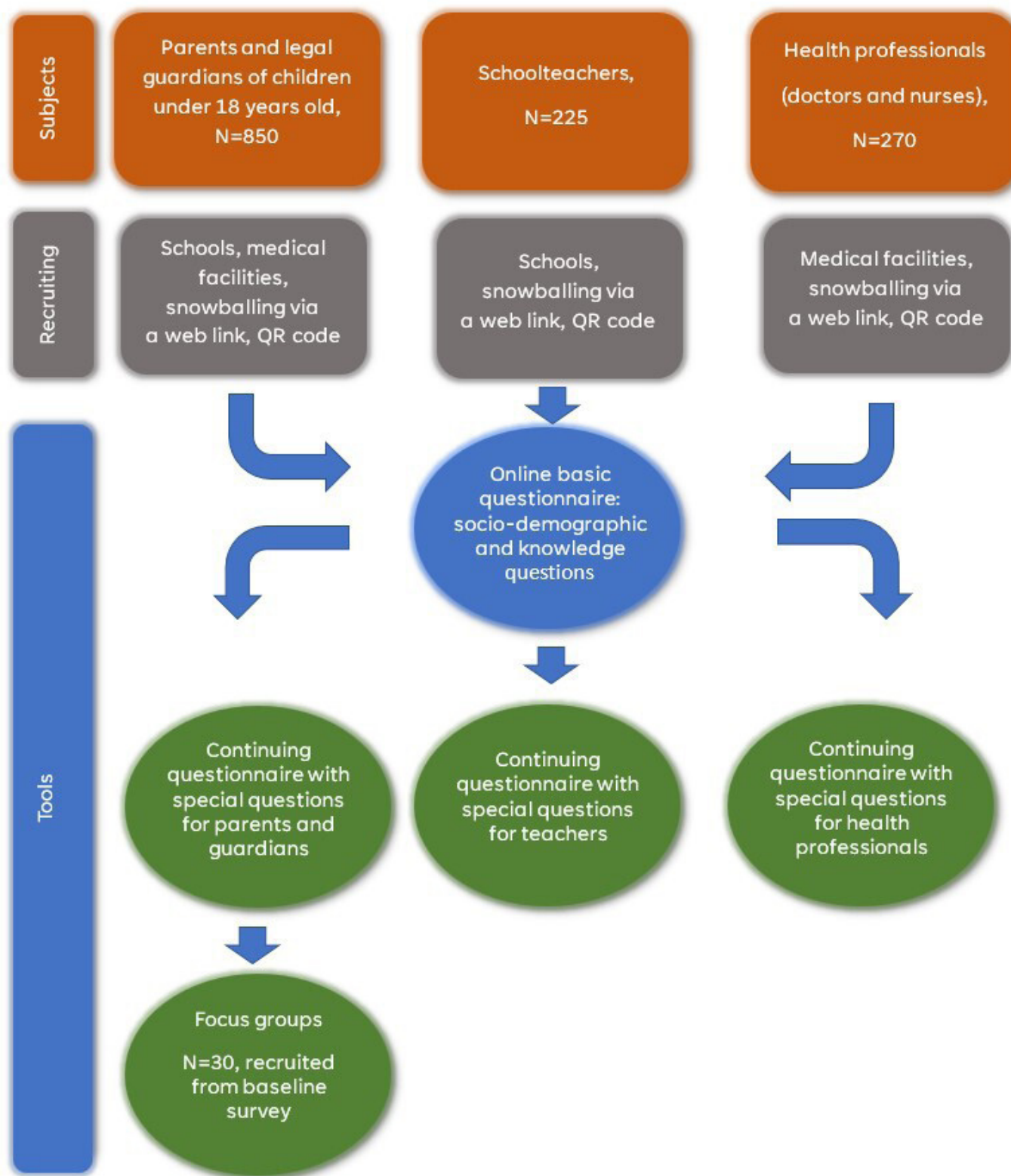
Figure 1 Research overview.

Determining the focus group sample size

In order to form four or five groups, a random sample of 30–40 parents or guardians of children under 18 years old will be drawn from those participants of the parental surveys who agreed to participate in the focus group discussions.

Data analysis
Quantitative study

Statistical analysis of primary data will be carried out using the IBM SPSS Statistics software (SPSS). Standard central tendencies of descriptive statistics (arithmetic

Figure 2 Settlements planned for the study on the map of Kazakhstan.

mean and CI, median, mode, SD) will be considered when analysing quantitative data on sociodemographic variables, knowledge, attitudes, intentions and barriers to HPV vaccination as well as data related to HPV vaccination communication. Answers to questions related to knowledge will be evaluated as follows: for correct answers or existing knowledge, one point is assigned; for incorrect answers or the answer 'I do not know', '0' is assigned. To check statistically significant differences in proportions depending on a number of comparison groups, we will use the Student's t-test criterion and the Mann-Whitney U test criterion to compare the averages in several groups, or a one-factor dispersion analysis of analysis of variance and Kruskal-Wallis will be used. Binary logistic regression will be used to assess the probability of using the vaccine based on the correlates of interest, including sociodemographic data, awareness, knowledge, sources of information and other variables. The OR with a 95% CI will be calculated. The next step is to perform a multivariate logistic regression analysis with the simultaneous input of all correlates from the previous analysis to calculate the adjusted OR. The principal component analysis will aid

Table 1	Inclusion and exclusion criteria of the study	
	Inclusion criteria	**Exclusion criteria**
Parental survey	Parent or legal guardian of children of both genders under 18 years of age	Parents or legal guardians of children 18 years or older
Survey for healthcare professionals	Employed health professionals (nurse or doctor) of any specialisation	Retired or unemployed healthcare professionals
Survey for schoolteachers	Employed schoolteacher, either primary or secondary	▶ Retired or unemployed school professionals ▶ Educational professionals of other than primary or secondary schools
All online surveys	▶ Access to the internet ▶ Willingness to participate	▶ Internet access limitation ▶ Unwillingness to continue the study
Focus group discussions	▶ Parents or legal guardians of children under 18 years of age living in the Republic of Kazakhstan ▶ Availability of informed consent ▶ Internet access for online meetings	▶ Internet access limitation ▶ Parents or legal guardians of children 18 years or olderLack of informed consent

Table 2 The main expected outcomes and methods of analysis of the study

Main outcomes and determinants	Method of analysis
Outcomes ▶ HPV vaccination hesitancy prevalence ▶ Level of knowledge about HPV, HPV-associated diseases, HPV vaccine ▶ Parental barriers to HPV vaccine acceptance ▶ Barriers to HPV vaccination recommendation among healthcare professionals and schoolteachers	Descriptive statistics
HPV, HPV-associated diseases, HPV vaccine knowledge determinants ▶ Sociodemographic determinants ▶ Information sources	T criterion and the Mann-Whitney U criterion, one-factor dispersion analysis of ANOVA, Kruskal-Wallis tests
HPV vaccination hesitancy determinants ▶ Sociodemographic determinants ▶ Knowledge and awareness of HPV, HPV-associated diseases, HPV vaccine ▶ Information sources ▶ Children's vaccination history, cervical screening history among women	Principal component analysis binary, multivariate logistic regression

ANOVA, analysis of variance; HPV, human papillomavirus.

in identifying the determinants of HPV vaccination hesitancy. The value of $p<0.05$ in bilateral tests will be considered statistically significant (table 2).

Qualitative study

The data from the focus group discussions will be digitally recorded, and content will be analysed using the software MAXQDA. The content will be analysed by a method of identifying, analysing and describing patterns (themes) in the data.[37] In the first step, the data will be transcribed and coded by two researchers who identify and group the contents by themes. Subsequently, the two versions of the coding will be compared and partially corrected. The second step will be a discussion with coauthors to reach a consensus and complete the analysis. The results of the analysis will be presented in the form of descriptions of individual participants' answers according to a question guide, as well as separate descriptions of trends in the development of discussions.

Research tools
Questionnaires

Data collection will be carried out using questionnaires developed for all three target groups based on similar studies and adapted for data collection according to the purpose and objectives of the study (figure 1).

Questionnaire development and validation

The development and validation of the questionnaires were conducted in a few stages. During the initial phase, the research group developed three types of questionnaires tailored for parents and legal guardians, teachers, and healthcare professionals, based on previous valid questionnaires.[29 38–40] Recognising the potential association between vaccine hesitancy and religious beliefs, three additional questions pertaining to religious beliefs and practices were included in the surveys.[41 42] In Kazakhstan, the re-launch of HPV vaccination is planned post-COVID-19 pandemic period, and attitudes towards COVID-19 vaccination can reflect the overall compliance with vaccinations, including HPV vaccination. In previous studies conducted in Kazakhstan, a high level of vaccine hesitancy towards the COVID-19 vaccine was identified.[43] To explore the possible relationship between attitudes towards COVID-19 vaccination and HPV, a question on attitudes towards COVID-19 vaccination was included in the basic questionnaire for all target groups. Building on previous findings that demonstrated the association between the source of information and awareness levels, this study aims to evaluate the impact of information sources as a factor influencing HPV vaccine hesitancy and to identify effective channels for public awareness during the introduction of the HPV vaccine.[31] To achieve this, additional questions were included in the survey concerning the sources of information about the HPV vaccine, the frequency of internet and social media usage, and preferred information sources. While acknowledging the sensitivity and societal taboo surrounding the LGQIA+ issue in Kazakhstan, and also considering the adherence to international research standards, it is important to clarify that questions related to gender identity diversity were intentionally excluded from the questionnaires. This decision was taken to mitigate any potential undesirable side effects that could compromise the research objectives.

After developing the questionnaires, a two-step translation process was performed to ensure linguistic equivalence and accuracy. First, the questionnaire was translated into Russian and then further translated into Kazakh by a certified translator (direct translation). Subsequently, the translated version was back-translated into Russian (reverse translation). This meticulous approach aimed to maintain consistency and validity between the two language versions of the questionnaire.

Following the language validation, a panel of five specialists in the fields of education, public health and clinical medicine, in addition to a focus group of parents, participated in the expert content validation process. The

experts meticulously evaluated the adequacy and validity of the questions, ensuring that they effectively addressed the research objectives and accurately measured the targeted constructs. After consulting with experts, the total number of questions for the three target groups was reduced from 112 to 81.

On successful completion of the expert validation stage, a pilot study was conducted involving 12 participants of each target group to examine the external validity of the questionnaire for acceptability and feasibility. The questions with initially unclear wording were updated. The average time spent answering the final questionnaires was 13.67 min for parents and guardians, 10.08 min for teachers and 12.83 min for healthcare professionals.

Questionnaire's structure

The proposed survey consists of a basic questionnaire for all participants and three special types of questionnaires for each target group (parents and legal guardians, healthcare professionals and schoolteachers). The basic questionnaire includes questions on sociodemographic characteristics, the history of vaccination and screening for CC in women, and knowledge about HPV and HPV-associated cancers. The questionnaire for parents and guardians comprises questions about attitudes toward HPV vaccination, hesitancy or intentions to vaccinate their children and barriers to HPV vaccination, available and preferred sources of information about HPV with characteristics of behaviour in the media space, and preferred communication modes for the invitation of adolescents to vaccination. In total, there are 54 questions in the parental questionnaire. The specific questions number 23 for health workers and 7 for schoolteachers.

The survey implies complete anonymity for respondents and can be administered in Kazakh and Russian. Prior to the survey, respondents will be acquainted with voluntary informed consent to the study in both languages (online supplemental appendix 1), including information about the researchers, the essence of the research, its main objectives, the guarantee of confidentiality and anonymity, security in participation, data protection and the expected duration of the survey. The administration of the survey will only be possible after informed consent has been obtained.

The questionnaire is compiled in simple language for easy comprehension, and the link is sent through available channels of communication. For convenience, respondents can stop and resume completing the questionnaire later if necessary. Respondents can only submit their response when they have answered all the questions on the questionnaire.

The basic questionnaire consists of two parts collecting data on sociodemographic characteristics and basic knowledge of HPV and HPV vaccination (figure 1). The first part of the basic questionnaire includes questions defining the sociodemographic characteristics of the respondents (online supplemental tables 1 and 2). For

female participants, three additional questions about the history of CC prevention are offered.

The second part of the common questionnaire assesses knowledge of HPV and vaccination against HPV. Responses to the 11 knowledge questions (online supplemental table 3) are assessed as follows: correct answers or existing knowledge are given a score of 1, while wrong answers or 'I don't know' are given a score of '0'. Question 10 offers 11 answer options, and there is an opportunity to choose several answer options, of which only five are correct (when shaking hands, through kisses, during sexual contact, during childbirth from mother to fetus, with bodily contact), five incorrect (through blood, through air, during pregnancy from mother to fetus, through water in the pool, through insect bites) and one option was 'difficult to answer'. Thus, the maximum score for all knowledge questions is 15, equivalent to 100%. Further, for parents and legal guardians, the questionnaire will continue with questions regarding attitudes toward vaccinations, barriers to vaccinations and communication. The first section includes questions on attitudes towards vaccination in general and childhood vaccination in particular (online supplemental table 3). The answers will help assess the level of confidence in vaccination in the Republic of Kazakhstan among different strata of citizens. The second section of the questionnaire includes questions examining barriers to HPV vaccination (online supplemental table 4). Because the HPV vaccine is targeted at adolescents of both sexes, differences in barriers for parents of boys and girls are assumed. To assess these, we included separate questions for parents of boys and girls. Examination of barriers will enable the design of key messages and responses to the most pressing issues in communicating with parents and legal guards during the HPV vaccination campaign, adapted for the Republic of Kazakhstan.

The final section concerns sources of information on HPV and HPV vaccination (online supplemental table 5). Responses to the questions of this block will give an understanding of the most demanded channels and ways of communication during the HPV vaccination campaign. In addition to communication channels, this block includes questions about the vaccination invitation process.

Specific questions have been developed for medical doctors and nurses to explore knowledge about vaccine administration, the vaccine recommendation process and counselling, and barriers to vaccine recommendation (online supplemental table 6). A special questionnaire for teachers includes seven questions about occupational characteristics and work experience, as well as questions about knowledge and practices about HPV and the HPV vaccine, and the willingness to recommend the vaccine to their students (online supplemental table 7). This study will reveal the intention to recommend HPV vaccination among healthcare professionals and teachers along with a variety of factors related to this intention. We assume that their knowledge and attitudes towards HPV vaccination

may be key predictors of their intention to recommend HPV vaccination.

Focus group discussion

We developed a topic guide to collect data in focus groups (online supplemental appendix 2). Since this vaccine is perceived as new for Kazakhstan, before the panel discussion, participants are given brief information in a few sentences about WHO recommendations regarding HPV-associated cancers and HPV vaccination. To answer the research questions, we included questions about parents' attitudes toward the introduction of the vaccine in Kazakhstan, the issues they are concerned about when deciding to vaccinate their children, what barriers they experience, and opposite facilitators to vaccinate against HPV. The discussion will also include questions about informing children about HPV and the vaccine and what modes of communication they feel are appropriate for their children. To gauge the development of the discussion, it will begin and end with the same question about willingness to vaccinate their children. Throughout the discussion, the moderator and the assistant encourage all parents to participate and ask for extended feedback. The focus group scenario can change slightly when particularly important topics are touched on, but the main points of the guide must be covered. Focus group discussions will be conducted in Kazakh or Russian.

Patient and public involvement

Acknowledging the significance and adhering to the principles of involving patients and the public in research, we incorporated public members into the study's design phase. We engaged a group of parents in a focus group to validate the content of the questionnaire, with their primary objective being the evaluation of the questions' relevance and clarity, the appropriateness of the questions, along with providing feedback encompassing both the questionnaire content and the study's overall framework. Following the conclusion of the study, our intention is to disseminate the findings to the participants.

ETHICS AND DISSEMINATION
Ethics of research

The study was approved by the Ethical Committee of the Kazakhstan Medical University 'KSPH' No. 138 of 31 May 2021.

Plan for the dissemination of the results of the study

The results of the study will be published in peer-reviewed scientific journals and will also be reported at national and international scientific conferences. Given that findings based on this study may be of interest to public education and influence public health policy, we will furthermore aim for the dissemination of the findings to national stakeholders, such as public health organisations.

DISCUSSION
Significance of the study

To ensure the successful introduction and acceptance of the HPV vaccine in Kazakhstan, especially after previous challenges, it is crucial to develop a comprehensive communication plan tailored to the society's specific needs. The findings from this study, conducted by interviewing a countrywide population sample of parents, health professionals and teachers, will enable an assessment of the necessity and extent of educational interventions and will help to design key messages for different communities in specific regions of the country. Understanding the preferred information sources and communication behaviour will guide the identifying effective communication channels during an information campaign among parents and legal guardians. The results on knowledge levels, barriers to recommending HPV vaccination, and factors influencing negative attitudes among healthcare professionals and schoolteachers will assist in the development of an educational strategy, equipping key sources to effectively disseminate accurate information about HPV, HPV-associated cancer and HPV vaccination to parents and adolescents. Equipped with these insights, health policy makers will have the necessary input to design an information campaign incorporating Kazakhstan-specific communication components, meeting the unique information needs of key stakeholders involved in the vaccination process. Therefore, equipping health policy makers with essential insights on the main components of communication will enable them to design a Kazakhstan-specific information campaign, tailored to the unique information needs of key stakeholders involved in the vaccination process. This, in turn, will ensure the success of the HPV vaccination programme and contribute to reducing the burden of cancer.

Strengths of the methodology

The involvement of different target groups in the survey that are assumed to be important stakeholders in the vaccination process is a strength of this study. Assessing the knowledge, attitudes towards the HPV vaccine, and barriers of each group in one period of time will give the most complete picture of these aspects in society. Using the online survey methodology improves the quality, speed and accuracy of the data collected, which is not inferior to a traditional paper survey.[44] Respondents' answers are recorded simultaneously in an Excel database, which eliminates errors on the part of researchers in the formation of the database. At the same time, not considering incomplete questionnaires excludes unmotivated participants and improves the quality of the study.

Due to the simplicity of the wording in the questionnaire, participants do not need to spend a lot of time on the answers, which contributes to a higher probability of completing the survey. Since this survey is conducted anonymously online and can be independently filled out at any convenient time, respondents have the opportunity

to answer honestly without fear of condemnation. This online survey can reach a large number of people and is performed without any time and financial cost for additional printed materials or people to conduct it. Among other things, participation in this kind of questionnaire in itself expands awareness of HPV and HPV vaccination.

A study in the form of focus group discussions can provide a broader understanding of barriers to vaccination, as parents will interact with each other during these discussions and provide more detailed explanations. In our opinion, a focus group is more appropriate for this purpose, as HPV vaccination is a completely new topic to parents, and the results can frame the discussion with the communities when vaccination programmes are introduced.

Possible limitations

To our knowledge, this is the first study in Kazakhstan that addresses several target groups in order to reveal inhibiting and supporting factors of HPV vaccination at an individual level. However, a few limitations of this study can be identified. One limitation may be the simultaneity of the study at that moment when a vaccine is not yet available and introduced in the country. It is expected that knowledge and opinion may change with increasing vaccination experience. Another limitation is the snowball sampling method in the online survey, which may affect the representativeness of the sample under study. The incorporation of medical and school organisations to disseminate questionnaires, along with an adequate sample size, can serve to counteract this limitation. Monitoring the diversity of respondents by place of residence, gender, occupation and other sociodemographic indicators will help to distribute of questionnaires also among underrepresented respondents. In our opinion, the benefits of reaching a broader spectrum of population groups may outweigh these limitations. The limitation of online surveys is primarily the availability of internet access, which can potentially influence sampling. Although internet access is widespread in Kazakhstan, there are still places where it is not available or is a financial burden for potential participants. The absence of interviewers in self-administered questionnaires may be a limiting factor, as interviewers help respondents to understand the structure of the questionnaire and the questions more easily. Another limitation of a survey using Google Forms can be attributed to the inability to calculate response rates, since the number of persons who receive the link is unknown.[45]

In our study, which primarily involves a survey, we acknowledge the possibility of certain risks occurring. Given that the study lacks the possibility of attracting additional recruiters, there might be challenges in recruiting respondents within the designated timeframe. To address this risk, the number of survey responses will be continuously monitored, and in case of lower-than-expected completed survey rates, an extension of up to 3 months may be considered for conducting the survey. To mitigate response bias, the questionnaire will include several validation questions and incorrect or inconsistent responses will be monitored and excluded from the analysis. For instance, in the parent's questionnaire, there will be specific questions to verify the presence of children, and if inconsistent responses are received, these questionnaires will be removed from the analysis. During focus group sessions, the interviewer effect may influence the type and quality of information obtained. To mitigate this risk, focus groups will be facilitated by research team members with training in qualitative research. Furthermore, to enhance data validity, audio recordings of the sessions will be made, allowing for discussions among study participants during the qualitative data analysis.

SUMMARY

Based on the published literature, there are limited studies examining barriers to the HPV vaccination programme in Kazakhstan. This study will identify social factors and knowledge gaps that limit vaccine acceptance among those involved, such as parents and caregivers, medical professionals, and school education professionals. Given past negative experiences with HPV vaccination in Kazakhstan, our proposed research will be important in forming a plan to introduce HPV vaccination in Kazakhstan, particularly the communication strategy and the need for training interventions for health professionals and teachers. It can also be used to assess which channels and methods of communication should be used in the HPV vaccination campaign. In addition, this study will shed light on the decision-making process of parents to vaccinate their children, which may provide insight into communication strategies when introducing the vaccine.

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