Bovine leukosis and the possibility to cause cancer in humans: A scientific review

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Summary

This review was made to explore the recent multiple studies on enzootic bovine leukosis, focusing on its prevalence, economic impact, the link with public health and the possibility to cause cancer in humans. The causative agent of enzootic bovine leukosis is a virus closely related to human T- cell leukemia virus (HTLV-1). The closeness between the two viruses helps the progress of cancer research in diagnosis and treatment, also the development of a vaccine in both human and veterinary medicine .The enzootic bovine leukosis is widely spread in the continents. The economic loses of enzootic bovine leukosis is related to the lowered productivity of effected cattle, morbidity, mortality and cost of control and eradication. This review proved that bovine leukemia virus is innocent from human cancer infection and there is no proof of virus living in human tissues. But this subject needs a lot of research to know the mechanism of the virus and its affects in cellular content of the organism.

Keywords: Enzootic bovine leukosis, Bovine leukemia virus, Carcinogenic retrovirus.

Introduction

Bovine leukosis is one of the most widespread types of neoplastic disease in dairy and beef cattle. This disease is divided into enzootic bovine leukosis (EBL), and sporadic bovine leukosis (SBL) (1). This disease was described at first time in 1871 in Lithuania, and was believed to be an infectious illness because it spread through herds of cattle. The first isolation of virus was in 1969 from cultured lymphocytes of cattle in an afflicted herd and identified as the agent of bovine leukosis (2). Bovine leukosis, bovine leukemia, lymphosarcoma, and malignant lymphoma are names given to the retrovirus disease. All of these terms refer to a neoplastic condition of tissues that affects the lymph nodes and lymphocytes, effect of true leukemia is rare. Bovine leukemia virus (BLV) has been investigated as an RNA genome delta retrovirus which is closely related to human T-cell leukemia virus (HTLV) (1). BLV causes large economic losses as a result a restriction on the exportation of cattle and their products from enzootic countries, in addition to eradicate carcasses, high morbidity, mortality and lowers dairy or beef production. Moreover the infected animals become highly susceptible to other infection and need high cost of treatment (3). A long time ago, there has been continuing controversy about the infection of human with BLV. Antibodies were found against this virus in human sera in 1981 (4). Many people in the U.S. were seropositive to BLV with other oncogenic viruses in chicken and turkey which had potential infectivity and oncogencity for human in vitro (5). In 2015 others, considered the exposure of human to BLV is a risk factor, and some thought there was a connection between BLV and breast cancer in human. The dairy products from infected cows were also associated with human mammary cancer However, others found the mammary cancer was associated with red meat practice, so red meat was considered a risk factor also (6-8).

BLV doesn't infect other animal species naturally, but it was reported that the virus can infect sheep and goat experimentally (9 and 10) also clinical signs and morphological changes happen in rabbits as encephalito - zoonosis (11). A benefit of this approach of studies (scientific reviews or meta-analysis) is the aggregation of information leading to a higher statistical power and more strong point estimate than the measure resulting from any individual study. However, making this analysis, the researcher obtains broad spectrum

ideas and make choices which can affect the results. They know how to search for studies, selecting studies based on a set of thought criteria, treating incomplete data, analyzing the data, accounting and impartiality of the publishing entity (12). The aim of this scientific review is to explore the recent multiple studies on enzootic bovine leukosis, the latest prevalence, economic impact, its relationship in public health and possibly to cause cancer in human

Materials and Methods

Many studies were identified as potentially relevant with the disease and a probability of cancer in human at the scientific web site such as Yahoo, Google, Google Scholar and Search Gate. Key words were used: Enzootic bovine leukosis (EBL), bovine leukosis virus (BLV), Middle East, carcinogenic retrovirus on the basis of the following: Indicates higher relative to BLV and EBL, the design of the study (cohort or case control studies). These two types are periodic surveys which can combat and eradicate EBL, then determined year of publication, place, (type, gender, age of animal) and diagnostic assays which were used to signify positive and negative results. Then, the data were extracted from these studies (Table, 1).

Table, 1: Studies (authors and year of established) ascending arrangement with countries and morbidity rate.

Studies (1976-2016)= 45		
Authors, year, (country) (Morbidity rate %)	**Authors, year, (country) (Morbidity rate %)**	**Authors, year, (country) (Morbidity rate %)**
Abt *et. al.* 1976 (USA) (5%) (13)	Nikbakht, *et. al.* 2010 (Iran) (15%) (28)	Junior *et. al.* 2013 (Barazil) (43)
Diglio *et. al.* 19 76 (USA) (59%) (14)	Mohammadabadi *et. al.* 2011 (Iran) (25%) (29)	Buehring *et. al.* 2014 (USA) (44%) (44)
Kenyon *et. al.* 1977 (USA) (50%) (15)	Ndou *et. al.* 2011 (South Africa) (13%)(30)	Gutiérrez *et. al.* 2014 (Argentine) (1%)(45)
Kettmann *et. al.* 1978 (Balgium) (89%)(16)	Mohammadi *et. al.* 2011 (Iran) (31)	Kobayashi *et. al.* 2014 (Japan) (74%) (46)
Kettmaan *et. al.* 1980 (France) (17)	Mohammadabadi *et. al.* 2011 (Iran) (32)	Mousavi *et. al.* 2014 (Iran) (24%) (47)
Kettmann *et. al.* 81(Balgium) (88%) (18)	Ababneh 2012 (Jordon) (33)	Nam *et. al.* 2014 (Russia) (1%) (48)
Onuma *et. al.* 1987(Japan) (90%) (19)	Dimttrov *et. al.* 2012 (Polgaria) (34%) (34)	Rajao 2014 (Brazil) (80%) (49)
Bender 1988 (USA) (52%) (20)	Avc *et. al.* 2013 (Turkey) (62%) (35)	Hernadnez *et. al.* 2014 (Colambia) (50%) (50)
Nelson *et. al.* 1988 (Barazil) (57%) (21)	Benavides *et. al.* 2013 (Colombea) (20%) (36)	Zaher and Ahmed 2014 (Egipt) (13%)(51)
Pyeon *et. al.* 1996 (USA) (54%) (22)	Giovanna *et. al.* 2013 (Colambia) (50%) (37)	Dolz 2015 (Costa Rica) (58%) (52)
Simard *et. al.* 2000 (Canada) (40%) (23)	Kanno *et. al.* 2013 (Japan) (50%) (38)	Mekata *et. al.* 20 15 (Japan) (4%) (53)
Hjart-ker *et. al.* 2001 (Norway) (10%) (24)	Moratorio *et. al.* 2013 (Uruguay) (39)	Nikbakht *et. al.* 2015 (Iran) (16%) (54)
Gillio-Tos 2007 (Italy) (37%) (25)	Murakami *et. al.* 2013 (Japan) (35%) (40)	Khudhair *et. al.* 2016 (Iraq) (8%)(55)
Kale *et. al.* 2007 (Turkey)(51%) (26)	Panei *et. al.* 2013 (Japan) (41)	Ma *et. al.* 2016 (China) (21%) (56)
Panie *et. al.* 2009 (Argentine) (83%) (27)	Tawfeeq *et. al.* 2013 (Japan) (33%)(42)	Farias *et. al.* 2016 (Argentine) (72%) (57)

The papers were supplemented with additional articles cited in its reference and were obtained by the electronic search only. Studies were selected, extracted data and analyzed by statistical program SPSS V.22. according to the principles as in following:

Acceptance studies conducted during the four decades (1976-2016) about EBL and BLV. Acceptance case control and cohort studies from randomly select 21 countries involve South and North two Americas, Asia, Europe, and Africa, which in this review formed case control 62% and cohort 38% (Tables, 2 and 3). Exclusion of studies that included case report, tissue culture, cell line, abattoir survey or review and the studies in the same country, time and design. Studies included living creatures like human, sheep and experimental animals in addition to cattle the natural host of BLV.

Table, 2: the studies of countries output from electronic search

Country	No. of studies	%
Japan	7	16
Iran	6	13.5
USA	6	13.5
Argentine	3	7
Colombia	3	7
Brazil	3	7
Turkey.	2	4
Belgium	2	4
Egypt ,Iraq, China, Bulgaria Canada, Jordan, Costa Rica, Italy, Norway, Uruguay, France, Russia, South Africa	13(one study in each one country)	2% each one=28% All of them
Total 21 countries	45	100

Table, 3: Frequency and percentage of studies according, the variables.

No.	Variable	F	%
	Types of studies		
1	cohort	17	38
	case. control	28	62
	total	45	100
	Ages		
2	>=15y.(human)	2	4
	more than 6 months (bovine)	7	16
	new born (bovine)	1	2
	34-50 years (human)	1	2
	more than 4 years (bovine)	6	14
	more than 2 years (bovine)	23	51
	total	45	100
	Gender		
3	male	1	2
	female	9	20
	both of them	35	78
	total	45	100
	Types of samples		
4	blood	35	78
	semen	1	2
	tissue	4	9
	Sera and milk	1	2
	total	45	100
	Types of beings		
5	human	5	11
	cattle	35	78
	lab animals	1	2
	mixed (cattle and sheep)	3	7
	another animals	1	2
	total	45	100
	Study related human cancer		
6	yes	10	22
	no	35	78
	total	45	100

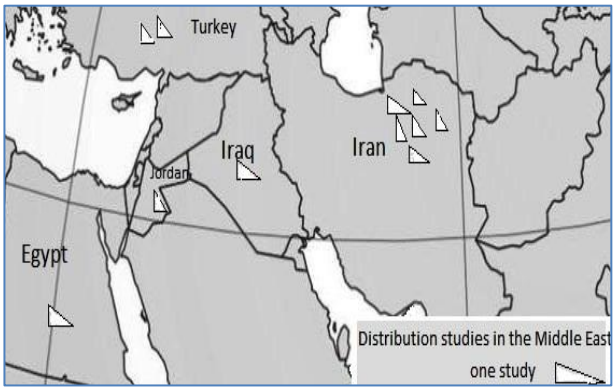
Distribution of BLV in the world: BLV infection is a wide extended disease in the continents, even though the virus is slowly spreading, many countries are enzootic (1). Data about (EBL) and causative agent in Iraq are very limited. Four papers were published (one of them by the electronic search and the other from an ordinary library by classic searching), first record in 1994 by the serological diagnosis of disease used agar gel immunodiffusion test (AGID) in Mosul (13), at that time around Baghdad area another study had found 7.1% seropositive in cases by ELISA assay (14). In 1997 a study reported that the seropositivety was 8.4% in imported cattle (Friesian) and 0% in local animals using ELISA assay too (15). Recently in 2016 a study in the middle Euphrates region detected the provirus 7.75% by Polymerase Chain Reaction (PCR) test (16).

In neighboring countries, the percentage of BLV infection is variable. In the north east of Iran the percentage of seropositive cases were 25% which was related to age of the animal or size and place of herds (17). Moreover a high prevalence of BLV was reported in southern of Turkey 59% it was found to be related with the number of lactations (18). In Syria the seropositive cases varied according to different tests such as 62.9%, 69.2% by AGID and ELISA respectively. In Jordan detected provirus by PCR (63.4%) while in ELISA test seropositive was 28.6%. In Saudi Arabia the seropositive cases were 39% in imported herds and lesser in breeding heifers (25%) which were confirmed by Immunodiffusion test (19 and 20).

About 50 years ago the disease was transferred through all European countries, lead to large economic and industry losses in cattle. Therefore, the making of a national program for (EBL) prevention and control was necessary. As a result of adequate monetary support and the firm act of the eradication program, now the disease has disappeared completely in most European countries like Belgium, Netherlands, Denmark, Germany, France, Great Britain, Austria and Finland. (21). The seropositive cases in Japan were 11.7% in 1980 (22). Now the seroprevalence of BLV infection in this country became 4.8%, this result of the effectiveness of the control and preventive programs (23). Infection remains endemic in many countries. BLV has a high prevalence in South America (24). The adverse economic impacts of BLV infection are rather not regular. However, they include death, culling, impacts on milk production, and barriers to international trade (25).

The Middle East (ME) has limited studies and the information from most countries was unavailable (Fig. 1), however, in these selected studies the Iranian seem 54.5% from (EM) studies and 13.5% from all collected studies (Table, 2). From these electronic searches, there is one study in each of Iraq, Egypt and Jordon 2% each one. Today screen studies are very important; especially there are tension and instability in this area that would accelerate extending the diseases from site to another. The samples or cases in selected studies (living creatures) were humans, sheep and, experimental animals like rodents in addition to domestic cattle (the natural host)

for BLV. The researchers isolated this virus from water buffaloes too (26 and 27).



Figure, 1: Distribution studies in the Middle East.

Experimental infections of BLV have been reported in many species, including rabbits (28), rats (29) chickens, pigs, goats (30) and sheep. However, only sheep consistently develop leukemia, more frequent and short latent period while rabbits present immune dysfunctions (but no tumors) (28 and 31). The virus was isolated just from cows with adult lymphosarcoma, and from cows with persistent lymphocytosis, but not from calf with, thymic, or skin forms of leukosis. The virus was not isolated from cattle affected by SBL (32).

In this review the studies used several types of specimen to identify the virus, by molecular and serological tests. The most sample used was blood 78% and the least were milk and semen by 2% each one. Although the serum was better for serological diagnosis, but other body fluids may be useful, such as milk and urine. The serological surveys estimate the Abs titer in blood and other tissue. Among the available commercial tests for detection of antibodies against BLV, milk ELISA is a popular method in large-scale herd surveillance, which has often been used for classification of herds as infected or non-infected (33). The weaknesses of testing milk for BLV antibodies would be the great dilution factor, the intervention by lactogenic proteins, and the unsteadiness of antibodies in store milk due to bacterial growth. Despite these problems, there are excellent causes to operate a milk-based antibody assay for BLV. This test is available and can save time and money (34). In this assessment most studies had used both sexes 78%, females 20% and male 2%. This is related to the dairy herd, most of them were females who live along productive age and EBL can affect and cause defects in aged animals after a long latent period (5 -10) years (2-4).

Methods of transmission: The virus is usually transmitted through contact with the blood of an infected animal. Only 0.0005 milliliter of blood is needed for the virus to infect the lymphocytes of healthy animals. BLV can be transmitted vertically (mother to calf) and horizontally (cow to cow) causing leukemia and multiple tumors from infected cattle by blood lymphocytes and other tissue yield (6 and 7). The calves of infected dams become infected with the virus at birth about 5 % but it is rather uncommon. Cows with a high virus and low antibody titer may transmit infection to their newborn, whereas cows with a low virus and high antibody titer are more likely to transfer immunity to their newborn. This immunity is only transitory. It results from colostrum antibodies that are temporary for few months (35).

Close contact, sucking insect vectors flies like horseflies and iatrogenic ways through the use of contaminated veterinary tools are all good sources of BLV diffusion from infected to non-infected cattle. The disease can be transmitted by milk-borne, artificial insemination, rectal palpation, contaminated surgical instruments (35 and 36). BLV can spread through castration, dehorning and breeding by natural way may also be a source of infection because blood may be transferred during copulation (37 and 38).

Clinical signs: Infection is silent, and many infected animals remain asymptomatic because the signs happen as a leukemic state or as persistent lymphocytosis. When an animal is in the clinical stages of leukosis, the disease is diagnosed by the presence of the tumors and/or general lymph node enlargement. About 5% of animals infected with (BLV) grow B-cell lymphoma or grow lymphosarcoma in various lymph nodes and organs after a long latent period. Cancer cells often penetrate many organs (Table, 4), including the abomasums, heart, uterus, mammary glands, and epidermal region of the central nervous system. Thus, clinical signs in cattle with lymphoma usually included loss of

body weight, decreased appetite, and reduced productivity (1 and 2). If the clinical disease is not present, the disease is called persistent infection, which is more general or persistent lymphocytosis (PL) which represents 30% of the infected animals (3).

Diagnoses: Bovine lymphoma or lymphosarcoma can be simply recognized by direct physical examination and by histo-cytological diagnoses of swollen lymph nodes when lymphadenopathy and obvious neoplastic changes in target organ are present (38). Rectal palpation is the best diagnostic tool to locate internal tumors if peripheral lymph node enlargement or exophthalmoses is not observed. Using the agar gel immunodiffusion (AGID) test, BLV infected cattle can be identified by testing sera for BLV antibodies. The virus often remains dormant in infected cows until they are stressed, such as during extremely hot or cold weather, parturition, or illness. However, when the number of cows condemned at slaughter plants is on the rise, it suggests that the number of infected cows is increasing nationally (3).

Clinical pathology: Serology tests for BLV virus using AGID or ELISA to detect seropositive or negative to infection, detect the provirus by PCR or use sheep bioassay lesions multicentric lymphoid tumor (1). In theses collected studies, ELISA assay was the most test used, only ELISA 25%, and combined with others assays 44.4% (Table, 5). Case control and cohort studies are the scope of EBL. There were six studies using agar gel immunodiffusion (AGID) test. The AGID test is one of the mainly dependable indicators of BLV infection. This test has a high level of specificity, suitable to the stability BLV genome. If the AGID test is unable to sense low levels of BLV antibodies rapidly after infection, ELISA or PCR can identify and confide. The four mainly usually used serologic tests for the bovine retroviruses are ELISA, AGID, indirect fluorescent antibody (IFA), and western blot (WB), but not all are available free or cheap (34 and 39).

Differential diagnosis: The disease must be distinguished from other diseases like, Lymphadenitis due to tuberculosis and Actinobacillosis, Congestive heart failure due to traumatic pericarditis, Fat necrosis, Compression of the spinal cord. Confirming the diagnosis occurs by serological and molecular technique methods (1).

Table, 4: Pathological and clinical pathology changes described in cases of the studies.

Types of cancer or cell body defect	No.	%
mixed cancer types	1	2.2
Enlarged lymph nodes	2	4.4
lymphoblastic leukemia, lymphoma	2	4.4
laryngeal/ hypopharyngeal carcinoma	1	2.2
breast cancer	4	9
neoplastic lymphocytes in peripheral blood	3	7
persistent lymphocytosis (PL)	2	4.4
titer of virus in the body	23	51
persistent lymphocytosis and the lymph node tumor	5	11
genotypic defect (expression gene in cell body)	2	4.4
Total	45	100

Table, 5: The main types of tests use in studies.

Types of tests	No.	%
ELISA (enzyme linked immunosorbent assay)	11	25
Electron microscopy, immunofluorescence, immunogold labelling demonstrating viral Tax protein, and PCR analysis	1	2
Southern blot technique	1	2
Nested liquid-phase PCR (Polymerase Chain Reaction) and DNA sequencing and immunohistochemical testing localized BLV	2	4
ELISA and AGID Agar Gel Immunodiffusion Test	3	7
IGG fluorescein conjugate	2	4
Nested PCR coupled with RFLP	2	5
Immunofluorescent tests	2	5
5 Exonuclease assay	1	2
Questionnaire	1	2
qRT-PCR (quantitative reverse transcription-PCR)	3	7
PCR AGID PHA	1	2
Immunofluorescent antibody technique and erythrocyte-antibody-Complement (EAC), rosette test	1	2
Gel transfer and filter hybridization	1	2
Cellular DNA hybridization.	2	4
Hematologic, serological and genetic tests	1	2
DNA extraction and PCR amplification &Sequence	2	4
ELISA qPCR	5	11
(ELISA) and agar gel immunodiffusion (ID) test	1	2
Agar Gel Immunodiffusion Test (AGID) and leukogram	1	2
Immunohistochemistry (IH) tests	1	2
Total	45	100

Control: Countries got a long way in eradicating disease and carried out great amount seroepidemiological studies, such as in the UK, France, Germany, Denmark, Spain over two decades ago. The Scandinavian

countries, Belgium, and the Netherlands, are officially free from EBL (7 and 34). Some other countries, such as Japan, the United States, and Argentina, have strongly been working on BLV troubles in current years to grow cost-effective plans for their dairy industries. Test and slaughter seropositive animals in herds using most common tests like ELISA as a screening test and retesting make herds free from virus. Quarantine the infected herds or all country very important to prevent spread of infection (39 and 40).

BLV and probability of cancer in human practically breast cancer: Although the molecular biology of BLV and its infection in animals is well-known, but little known about the probability of BLV infections in humans. (40-42). Infected cows possess BLV infected cells that are present in marketed beef and dairy products. It has been demonstrated that viruses present in bovine eatable products may not be completely inactivated by pasteurization or cooking (43). Oral transmission of the closely related HTLV has been described in humans, suggesting the potential for oral transmission of BLV in humans (44). No final evidence exists that BLV is transmissible to humans, pasteurization destroys the virus easily, and it can live only a few hours at room temperature outside of living cells. Families that consumed raw milk constantly were found free of BLV infection, in addition, veterinarians and others who work closely with BLV positive blood on a daily have not been infected (45 and 46).

Several researches tried to link the BLV and human health, especially breast cancer. Studies about the possible routes of infection and to explain the genetic transformation processes in humans are raised. A number of researchers in one study examined tissues for breast cancer from 239 women, and evaluated them with tissues pinched from other women who have no history of breast cancer. They found that 59% of the cancerous tissue and 29% of women without cancer are exposed to this virus. In our analysis 22% from all collected studies were conducted about this object but the newer studies refuted the existence of any relationship between the virus and cancer in humans (47 and 48).

Conclusion: The high prevalence of the BLV in countries, the consumption of milk, meat and animal products which are positive for the disease, the prolong exposure to the virus, the immune response against it, possibly confirm the presence of the virus in the human genome, all these things mean that there is a real problem. It is necessary to rethink a new vision for human health as programs of diagnosis, prevention, control and eradication of the virus, chiefly in high prevalence countries. These actions lead to reactions like reduction in contact with a virus and then reduce the risks of zoonosis effects.

The possibilities of action of any virus in humans and animals like benign, pre-malignant and malignant cell changes or latent virus in healthy patients could be found without observing changes in tissue were shown in several previously mentioned reports as in HIV and HTLV.

A change of thinking on the relationship between cancer and viruses is necessary. There is a mystery (various hypotheses) could be resolved. However, new lines must be opened with ways that allow a better understanding of the action of the virus, particularly BLV and cancer in humans. New accurate diagnosis, prevention and control methods of these diseases will continue to develop. Breast cancer occupies a significant position worldwide in terms of morbidity and mortality. Between 5 and 10% of all breast cancer cases are associated with hereditary factors. The rest is associated with other factors such as infections, of which 8% of the malignancy are reported in developed countries and an impressive 23% in developing countries.

Recommendations: Scientific focus can estimate the severity of the disease in several countries and predisposing factors which can plan a roadmap for controlling and eradicating the disease. We suggest that more studies are done to provide sufficient evidence by the virological and seroepidemiological measure relating BLV and human health. We need a new mind setting to understand this relationship. To prevent, control and eradicate EBL, reduce BLV transmission as in following procedures: Reduce number of biting insects, test all cattle entering the herd for BLV, and

isolate them for 30 to 60 days, do not use colostrum or milk from BLV positive cows. Feed calves milk replacer or pasteurized milk when BLV-free milk is not available, use BLV-negative bulls or semen for all breedings, use bloodless dehorning methods, such as electric, hot iron, or caustic paste, implement annual testing for all animals, sterilize calf delivery equipment between uses and clean feed and water containers regularly to reduce blood contamination.

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ابيضاض الدم البقري واحتمالية تسببه بالسرطان في الإنسان: مراجعة علمية

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الخلاصة

صممت المراجعة للتحري عن دراسات عديدة أجريت عن مرض ابيضاض الدم البقري المتوطن، وتسليط الضوء على مدى انتشاره والتأثير الاقتصادي له وعلاقته بالصحة العامة وامكانية تسببه بالسرطان لدى الانسان. إن العامل المسبب لهذا المرض هو فايروس ذو ارتباط وثيق بفيروس خلية تي لسرطان الدم البشري (HTLV-1). وقد ساعدت العلاقة الوثيقة بين الفيروسين في تطور بحوث السرطان في مجال التشخيص والعلاج وتطور اللقاح في كل من الطب البشري والبيطري. ان هذا المرض ذو انتشار واسع في عموم القارات والخسائر الاقتصادية الناجمة عن هذا المرض تكمن في انخفاض انتاجية الماشية وشدة الإصابة ومعدلات الوفيات والمبالغ الطائلة التي تنفق من أجل السيطرة وكبح جماح هذا المرض. أثبتت هذه المراجعة التجميعية بأن فايروس ابيضاض الدم لايمت باي صلة لإصابة الإنسان بالانواع السرطانية كما وانه لايوجد أي دليل على وجود الفايروس الحي في الأنسجة البشرية .لكن هذا الامر يحتاج مزيد من البحث في آلية امراضية الفايروس وتأثيره في المحتوى الخلوي للكائن الحي.

الكلمات المفتاحية: ابيضاض الدم البقري المتوطن، فايروس الابيضاض البقري، الفيروسات القهقرية المسرطنة.