The cervical cancer vaccine in Ireland: Well worth the wait

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CLINICAL POINTS

- Cervical cancer results in approximately 300,000 deaths worldwide per annum and is the third most common cancer in women.
- Over 99% of cervical cancer histological specimens incorporate Human Papilloma Virus (HPV) DNA.
- HPV 16 and 18 are the strains most commonly implicated in the development of cervical cancer.
- Currently, CervicalCheck offers free papanicolaou smears to women in Ireland for the early detection of pre-cancerous lesions and cervical carcinoma; widespread vaccination has the potential to further reduce cervical cancer deaths.
- Two vaccines offer protection against HPV: Gardasil (HPV 6,11,16,18) and Cervarix (HPV 16,18); clinical trials have demonstrated the efficacy of these vaccines for up to 5 years.
- A report in Ireland by the Health Information and Quality Authority (HIQA) indicated that introduction of HPV vaccines into a national immunisation programme, in conjunction with regular papanicolaou smear screening, would be cost effective.

ABSTRACT

Cervical cancer is the third most common cancer in women and results in approximately 300,000 deaths worldwide per annum. Research has uncovered that infection with particular types of the human papilloma virus (HPV) is the strongest independent risk factor for the development of cervical carcinoma. Due to this relationship, vaccines against the foremost carcinogenic strains of the virus were developed in hopes that they would prevent the subsequent development of malignancy. Two vaccines currently exist: the quadrivalent vaccine, Gardasil and the bivalent vaccine, Cervarix. Both vaccines target the two Human Papillomavirus strains that are most commonly associated with the development of cervical cancer, types 16 and 18. The Gardasil vaccine also targets Human Papillomavirus types 6 and 11, which are commonly associated with genital warts. Five-year follow-up studies have shown both vaccines to be over 90% efficacious. There is, however, a lack of long-term data on both vaccines and more research is necessary to further evaluate their long-term outcomes on the prevention of malignancy. Currently, the major protection offered to women in Ireland against cervical cancer is that of secondary prevention via regular screening with the papanicolaou smear. A vaccine campaign is due to commence later this year, with the introduction date currently set as September 2010. It is expected that immunisation against the Human Papillomavirus in combination with regular papanicolaou smear screening will result in a reduction in the incidence of cervical cancer in Ireland. In this review, the link between cervical cancer and the Human Papillomavirus will be discussed in addition to providing support for the introduction of the Human Papillomavirus vaccines into the Irish immunisation schedule.

INTRODUCTION

Cervical carcinoma is the uncontrollable growth of cells in a woman's cervix and is the third most common cancer in women resulting in 300,000 deaths worldwide per annum[1]. In Ireland, there is an average of 180 new cases of cervical cancer diagnosed each year with an incidence of 23.64 per 100,000 women[2]. Furthermore, cancer of the cervix results in 73 deaths annually in Ireland with an average age of mortality of 56 years[2].

Infection with human papilloma virus (HPV) is a critical factor in the development of the majority of cases of cervical cancer. One study found that over 99% of cervical cancer histological specimens had incorporated HPV DNA[3,4]. HPV infects cervical cells via integration of its viral DNA into the host DNA, disrupting key protective proteins of cervical cells and up regulating viral proteins[5]. The result is cells with malignant potential, liable to cause cancer if they are not detected early and treated.

There are many different strains of HPV with some types being more carcinogenic than others. HPV 16 and 18, in particular, are considered high-risk strains and have been implicated in up to 77% of cervical cancers in developed countries[6]. Within Ireland, studies on the prevalence of HPV 16 and 18 found that of those women infected with HPV, 31.5% were infected with HPV 16 and 12% were infected with HPV 18[7,8]. Despite this high prevalence, women in Ireland remain unprotected against these two strains of HPV.

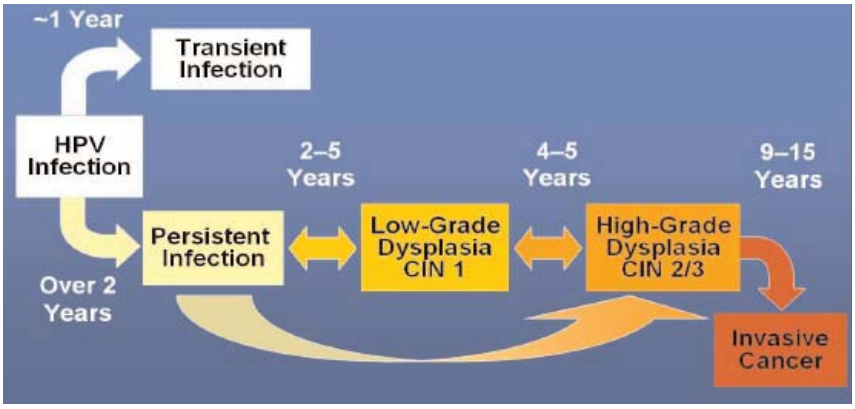
Currently, a screening programme is in place for the early detection of

cervical dysplasia. The National Cervical Screening Programme, 'CervicalCheck', was introduced in Ireland in September 2008. This programme targets 1.1 million eligible women aged 25 to 60 years old and is expected to result in a 91% cumulative risk reduction in the incidence of cervical carcinoma[1]. Under this programme, free cervical screening with a papanicolaou (pap) smear test is offered every three years for women aged 25 to 44 and every five years for women aged 45 to 60[9]. CervicalCheck does not incorporate a vaccine against HPV as part of its programme and therefore, does not prevent HPV infection at its outset.

The long-term outcomes of vaccination against cervical cancer have not been fully elucidated and more research is needed to assess the effectiveness of both commercially available vaccines. However, it is expected that immunisation against HPV in combination with regular pap smears will result in a further reduction in the incidence of cervical cancer. The aim of this article, therefore, is to discuss the potential benefits of introducing a vaccine against HPV in Ireland by reviewing the literature supporting their use with regards to both efficacy and cost effectiveness.

Cervical Cancer

Cervical cancer is primarily a neoplasm of the squamous cells of the cervix, the inferior part of the uterus[5]. The cervix is lined by both columnar and squamous epithelium, which meet at the squamocolumnar junction. During certain times in a woman's life, this junction shifts, under the influence of hormonal factors, exposing some of the columnar cells to the more acidic environment of the vagina[5]. As a result, some of these columnar cells undergo metaplasia or transformation to squamous epithelium. Cervical cells undergoing metaplasia are more susceptible to infection with HPV[5].



▲ **Figure 1:** This schema shows the relationship of a HPV infection and potential outcomes, with the probable timeline dependent on the individual's immune reaction to HPV. Source: Pagliusi[12]

Once infected with HPV, cervical epithelial cells show different characteristics compared to normal cells. Cells infected with HPV are more disorganised, they show enhanced mitotic activity, as well as nuclear pleomorphisms[5]. Cervical intraepithelial neoplasia (CIN) is the term used to describe this dysplastic change, and is considered a pre-cancerous lesion as this dysplasia can progress to malignancy[5]. The location of the dysplasia determines which type of CIN is present[5]. CIN 1 occurs when the abnormal cells are restricted to the lower third of the epithelium of the cervix. CIN 2 occurs when two thirds of the epithelium is involved, while CIN 3 occurs when the abnormal cells make up greater than two thirds of the cervical epithelium[5]. Stage 1 cancer occurs when there is invasion of the stroma of the cervix by these dysplastic cells[5]. For invasive carcinoma to occur from CIN 1, it usually progresses through to CIN 2 and subsequently CIN 3. However, not all cervical cancer progresses in this way, with 20% of CIN 2 and CIN 3 developing de novo[5].

Research has uncovered many other risk factors that are associated with the development of CIN and subsequent cervical cancer. These factors include early age at coitarche, multiple sexual partners, unprotected sexual intercourse and low socioeconomic status[5]. However, infection with HPV has been consistently implicated as the main aetiological agent in the development of cervical intraepithelial dysplasia and ultimately cervical cancer[5]. Factors such as cigarette smoking and immunodeficiency contribute to the development of cervical cancer by impairing immune clearance of HPV[5].

HPV and the Link to Cervical Cancer

HPV is recognised as the main cause of cervical intraepithelial dysplasia. HPV belongs to the Papillomaviridae family and is a non-enveloped icosahedral virus of circular, double-stranded DNA. HPV infects the cells of the cervix via integration of its viral DNA into the host DNA of cervical cells. During integration, viral E2 is disrupted, which is a key protein in the oncogenicity of HPV[10]. E2 is a transcriptional repressor of viral oncogenes E6 and E7 and its degradation thus leads to their up regulation[10]. Protein E6 binds to p53 promoting its proteolysis and thereby preventing virally infected cells from apoptosing. Protein E7 binds to pRb, an inhibitor which prevents growth of the virus within host cells. E7 degrades pRb,

which is no longer able to exert its action, thus promoting DNA synthesis of the virus within the host cells[11].

The integration of viral DNA into the cells of the cervix is a catalyst for the development of cervical cancer as they now have the ability to undergo dysplastic change[5]. The evolution to malignant cells takes approximately 9-15 years with the intermittent stages (CIN) detectable via the pap smear[5]. The typical progression of cell changes with time is illustrated in Figure 1.

The National Cervical Screening Programme: "CervicalCheck"

Free cervical screening under CervicalCheck was introduced in September 2008 and is offered to women in Ireland that satisfy certain criteria. Screening consists of a pap smear in which an endocervical brush is used to collect cells from the outer cervical opening, known as the os. These cells are kept in a liquid medium before being placed on a glass slide and examined microscopically for dyskaryosis. A smear is recommended every 3 years for women aged 25 to 44 and every 5 years for women aged 45 to 60. Screening is not warranted in those over 60, unless the woman has never had a previous smear. If a smear result is abnormal, a follow-up is arranged according to the CervicalCheck protocol. If CIN 1 is suggested cytologically, a repeat smear is advised in 6 months to check for progression. If CIN 2/3 is suggested, referral to colposcopy (cervix viewed more closely under microscope) is recommended[9].

Pap smear screening is the basis of CervicalCheck as it successfully enables detection and treatment of pre-invasive lesions and low-grade cancers, before they progress to invasive cancer[12]. With the advent of cytological screening programmes, the incidence of cervical cancer in the developed world has been significantly reduced. The American Cancer Society has cited that pap smears have reduced the death rate in the United States to one third of its value 50 years ago[13]. Despite the success of pap smear screening, however, there is still a high incidence of cervical cancer. The Irish Cervical Screening Research (CERVIVA) Consortium in 2009 reported a HPV prevalence rate of 18% in a population of 1,300 women screened[2]. The continued high incidence of cervical cancer despite the use of pap smear screening emphasizes the need for the introduction of a vaccination programme.

The HPV Vaccine: Structure, Function and Mechanism of Action

Vaccines against HPV were developed with the hope that, in combination with pap smear screening, they would lead to a significant reduction in the morbidity and mortality of cervical cancer. Currently, two vaccines have been developed and clinically evaluated, the quadrivalent vaccine, Gardasil, and the bivalent vaccine, Cervarix. Both vaccines target the two most common high-risk HPVs, types 16 and 18, while Gardasil also targets HPV 6 and 11 (responsible for >90% of genital warts). Results from clinical trials indicate that the vaccines are safe, well tolerated and highly efficacious in HPV naïve women[6].

Both vaccines are adjuvant non-infectious recombinant vaccines prepared from highly purified Virus-Like Particles (VLPs) of the relevant HPV viruses. VLPs contain the major capsid protein L1 without the viral DNA needed for replication. Thus, they are serologically indistinguishable from natural viral capsids but lack viral nucleic acid and are therefore non-infectious. Gardasil uses an aluminium-based adjuvant, whereas Cervarix uses the proprietary adjuvant ASO4. The difference in the adjuvant base of the two vaccines has been noted to affect immunogenicity. Clinical trials have demonstrated stronger antibody responses against HPV 16 and 18 in ASO4-based vaccines when compared to the aluminium-based vaccines[14]. Furthermore, higher titres of HPV L1–specific B cells were noted in the ASO4 adjuvant group[14]. It is unclear yet as to whether this will confer enhanced efficacy or a longer duration of immunity thereby necessitating further evaluation.

The mechanism of action of the vaccine has been elucidated using animal studies with analogous papillomaviruses. These studies have deduced that the efficacy of L1 VLP vaccines is mediated by the development of a humoral immune response. Studies in animal models have demonstrated that these L1 VLPs induce high titres of neutralizing serum antibodies, particularly Immunoglobulin G (IgG), which protect against cutaneous and mucosal papillomavirus challenge[14]. Both Gardasil and Cervarix have demonstrated immunogenic potential via their production of specific neutralizing antibodies.

Suggested Use and Efficacy of the HPV Vaccines

Current guidelines set up by 'The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices' in America, exist for the use of the HPV vaccine. Both vaccines are administered in 3 separate doses over a 6 month period. Cervarix injections are administered at 0, 1 and 6 months, while Gardasil administration occurs at 0, 2 and 6 months. Three doses are necessary to confer immunity with the vaccine, with maximal efficacy achieved 1 month after the final dose[6]. The current recommended ages for administration of the vaccines are 10-25 years for Cervarix and 9-26 years for

Gardasil, ideally pre-coitarche. The optimal target age of vaccination is 10-15 years. These indications are the result of two studies; Pedersen et al 2007 and Block et al 2006 showed a higher antibody titre in girls given the vaccines at 10-15 years of age versus those given the vaccine at 15-25 years of age[15,16]. The higher antibody titre is expected to confer a longer duration of protection.

Studies investigating the effectiveness of both vaccines in the prevention of CIN and the development of cervical cancer have been undertaken. Gardasil, the quadrivalent vaccine, has been approved for the prevention of cervical cancer and CIN 2/3 related to HPV 6, 11, 16, 18[17]. To investigate Gardasil's effectiveness, four placebo-controlled, double blind, randomized control trials have been conducted. These included two Phase I trials: Protocol 005 and Protocol 007 and two Phase III trials: FUTURE I & II (Females United To Unilaterally Reduce Endo/Ectocervical Disease). FUTURE I & II and Protocol 007 evaluated the full quadrivalent vaccine while Protocol 005 investigated only the HPV 16 portion of the vaccine. Included in the studies were 20,541 women aged 16-26 in 29 different countries. Inclusion criteria were those who were HPV 6, 11, 16, and 18 naïve at onset, remained negative for HPV through to month seven, and completed the 3-dose course of the vaccine within 1 year. In all four trials, subjects received doses on day 0, at 2 months and again at 6 months. Combined data from the four trials, after an average follow-up of 3 years, indicated a significant reduction in the number of HPV 6, 11, 16 and 18 associated cases of CIN. The results were 0 new cases of HPV 16 or 18 related CIN 2/3 versus 53 cases for placebo, conferring a 100% efficacy. For HPV 6, 11, 16 and 18 related CIN1/2/3, 4 new cases were found versus 83 for placebo, yielding an efficacy of 95.2%[18].

Cervarix, the bivalent vaccine, has been approved for the prevention of cervical cancer and CIN 2/3 related to HPV 16 and 18[10]. The efficacy of Cervarix was assessed in two placebo-controlled, double blind, randomized control trials, one Phase II trial and one Phase III trial. A total of 19,778 women aged 15 to 25 years were studied. In the Phase III trial, the PATRICIA study, the efficacy of Cervarix was analyzed in the total vaccinated cohort[19]. The efficacy of Cervarix in the prevention of CIN 2 associated with HPV 16 and/or HPV 18 was assessed at 14.8 months following the last dose of the vaccine or control. This study showed a significant reduction in the number of HPV associated CIN cases, with 2 new cases of CIN 2 or greater in the vaccinated cohort versus 21 new cases in the placebo group, conferring a 90.4% efficacy[19].

The statistically significant reduction in cases of CIN 2 and CIN 3 associated with the administration of Gardasil and Cervarix is expected to lead to a reduction in the incidence of cervical carcinoma. However, it is not known at this time the length of protection that either of these vaccines will confer. Gardasil has demonstrated clinical efficacy for up to 5 years against HPV 6, 11, 16 and 18. Recently available data has indicated that Cervarix is highly efficacious in preventing most CIN 2 lesions caused by HPV 16 and 18 for up to 5.5 years [20]. In addition, some studies suggest that a continued cross-protection against HPV 45 and HPV 31 infections may also exist with Cervarix[20]. It is unknown whether or not a booster will be required to maintain immunogenicity. Therefore, continued surveillance of vaccinated individuals is necessary to assess the entire length of protection. The length of immunity conferred and the possible need for a booster are important aspects in assessing the long-term cost effectiveness of the vaccines.

Cost Effectiveness of the HPV Vaccines

The cost effectiveness of introducing a vaccination programme against HPV in Ireland has been a continued topic of debate and was recently examined in a report called "The Role of Human Papillomavirus Vaccines in Reducing the Risk of Cervical Cancer in Ireland," that was published by the Health Information and Quality Authority (HIQA). In this report, the cost effectiveness was calculated based on the cost of vaccination minus savings on unneeded treatment, due to prevention of HPV 16/18 dyskaryosis and neoplasia. Another consideration of the cost effectiveness calculation was the morbidity prevented. The decrease in morbidity expected was based on the number of cases of CIN 1, 2/3 and invasive carcinoma in 2004. Results were expressed as Incremental Cost Effectiveness Ratios (ICER) per Life Year Gained (LYG). An Incremental Cost Effectiveness Ratio (ICER) is the difference between the cost of the new treatment and the current treatment, divided by the difference between the effect of the new treatment and that of the current treatment. A Life Year Gained (LYG) calculates the difference in the cost of having a vaccination programme, compared to the cost of having no vaccination programme, divided by the average difference in survival (in years) across the population at which you are looking, allowing one intervention to be compared with another.

Vaccinating 12 year old girls against HPV 16 and 18 was found to have an ICER of approximately €17,383/LYG[6]. Had the benefit to quality of life associated with the prevention of malignancy been included, this figure would be lowered further[4]. This is a favourable result considering that the usual threshold for the provision of drugs in Ireland is €45,000/QALY

(Quality Adjusted Life Year)[6]. A LYG does not take into account the quality (in terms of health status) of the year of life gained whereas a Quality Adjusted Life Year (QALY) is a measure of the year of life adjusted for its quality. A year in perfect health is considered equal to 1.0 QALY. The HIQA report showed the HPV vaccine to be more cost effective than the universal hepatitis B vaccination in Ireland (€37,019/LYG)[6]. If the catch-up vaccination for 13 -15 year olds was also to be included in the programme, this would raise the ICER of annual vaccination to €52,968/LYG which exceeds the threshold[4]. However, if quality of life gain was included in the analysis, (expressed as a QALY) this addition would likely also be rendered cost effective[6].

Vaccination of 12 year old girls as outlined in the HIQA study will begin in September 2010.[6]. This programme will also include a once-off catch-up vaccination for 13 -15 year old girls. Although it will take at least 15 years after implementation of the programme before monetary savings will begin to be seen it is none the less economically justifiable. Vaccination of young females in Ireland would not only prevent the anxieties that accompany a diagnosis of CIN but also the subsequent development of sequelae.

Limitations and the Future

Both the quadrivalent and bivalent HPV vaccines have limitations. There are more than 100 different types of HPV and at least 15 of them are oncogenic for which no immunity is provided[21]. Although it is estimated that HPV 16 and 18 cause 71% of cervical cancers, a further 29% of cases are attributed to non-vaccine protected strains[21]. The development of a vaccine that incorporates these additional strains is a possible future development.

Another limitation of the HPV vaccines is that the 5.5 year follow-up study for Cervarix and the 5 year follow-up studies for Gardasil may not be long enough for cervical cancer to develop. However, with the prevention of CIN 2/3, it is believed that the subsequent development of malignancy is unlikely. Ongoing long-term studies are needed to assess the true effect in the reduction of the incidence of cervical carcinoma in the vaccinated cohort.

Finally, Gardasil and Cervarix do not prevent HPV infections already present at the time of vaccination from progressing to cancer, stressing the continued need for cervical screening[22]. Laboratory research and several human clinical trials are currently ongoing for the development of therapeutic HPV vaccines that could possibly eliminate existing HPV infection[23].

Conclusion

The national screening programme plays a pivotal role in reducing the incidence of cervical cancer, however, cancer of the cervix still remains a highly prevalent gynaecological cancer. HPV types 16 and 18 have been implicated in 70% or more of cervical cancers. With the advent of the HPV vaccines against these strains, it is possible to have a primary prevention programme to prevent neoplastic lesions from the outset[6]. Cervarix and Gardasil vaccines, which target both of these high-risk viruses, have been introduced in a number of countries over the past few years. The ability of both vaccines to prevent CIN 2/3 in pre-coital females and the cost effectiveness by which this can be achieved indicates that HPV vaccination would undoubtedly be a beneficial addition to the Irish healthcare system. According to the National Cancer Institute, "Widespread vaccination has the potential to reduce cervical cancer deaths around the world by as much as two-thirds if all women were to take the vaccine"[2]. The vaccine, however, does not eliminate the need for scheduled cervical cytology and it is essential that the vaccine be combined with regular cervical smears in order to gain the maximum synergistic benefit.

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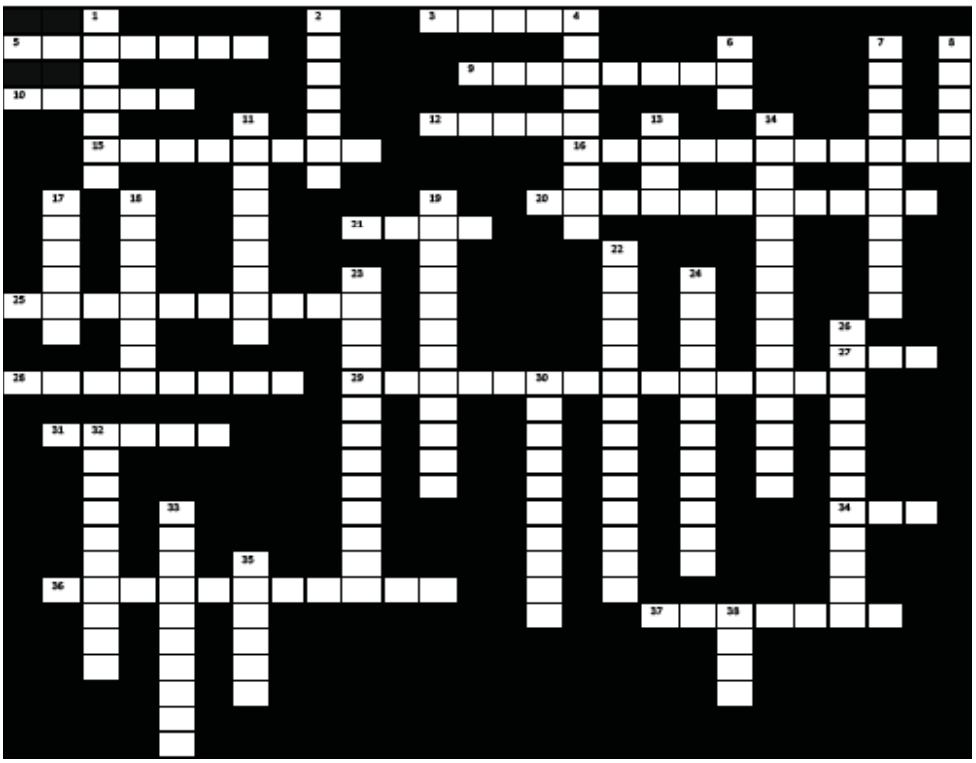

SOLUTION ON PAGE 89

ACROSS

3 **Postulates.(5)**
5 **Psoriasis is associated with this phenomenon.(7)**
9 Famous German Surgeon (8)
10 Earth (5)
12 **Wolff-Parkinson-White syndrome has this classic wave on E.C.G. (5)**
15 **Rupture of the middle meningeal artery may cause this haematoma.(8)**
16 **Form of focal dystonia following neuroleptics administration.(11)**
20 Spots in the iris of a Down Syndrome child.(11)
21 **This infection can cause spleenomegaly after kissing.(4)**
25 Antidote for malignant hypertension.(10)
27 Triplet repeated in Hungtinton's disease. (3)
28 **A syndrome characterized by postpartum hypopituitarism.(9)**
29 This antipsychotic can cause agranulocytosis. (15)
31 Second cranial nerve (5)
34 **Subsequent to a gastrectomy it is important to supplement the patient with this vitamin.(3)**
36 Bilateral lymphadenopathy and erythema nodosum would be suggestive of this diagnosis.(11)
37 **This clinical sign can be present with invasion of the sympathetic chain. (7)**

DOWN

1 **A type of prescription used to prevent antibiotic resistance. (7)**
2 **This fossa contains brachial contents.(7)**
4 **Type of conduction in myelinated nerves.(9)**
6 **The main psychoactive substance found in the Cannabis.(3)**
7 Cells promote the production of renin.(6,5)
8 **An important cycle in glucose metabolism.(5)**
11 **This type of breathing is associated D.K.A. (8)**
13 Palsy attributable to macrosomia.(4)
14 **Common infectious organism found in Lake Victoria.(15)**
17 Nerve that supplies the triceps.(6)
18 **If the hallux dorsiflexes this is a..... Babinski's sign.(8)**
19 **Spleenectomised patients are at increased of infection from this type of bacteria.(12)**
22 **"Shutter Eye".(9,5)**
23 Young Red Blood cells(13)
24 **A deep depression in the upper surface of the body of the sphenoid bone. (5,7)**
26 **1st choice antihypertensives in diabetics.(3,9)**
30 Causes slapped cheeks. (10)
32 **Painless jaundice and a palpable gallbladder in a patient is suspicious for this malignancy.(10)**
33 **The most lethal form of malaria.(10)**
35 **This score is use to predict whether induction of labour will be required. (6)**
38 Mature treatment for T.B.(4)