UNIT NO. 4

CERVICAL CANCER VACCINES

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ABSTRACT

This article endeavours to present the data and current understanding of the HPV vaccines in a consolidated manner and hopes to clarify some 'conflicting' issues or understand the basis of their existence in the first place.

KEYWORDS: Cervical cancer vaccine, HPV, Immunogenicity, Vaccine efficacy

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INTRODUCTION – ARE WE CONFUSED ABOUT THE DATA?

1) Following the widespread introduction of the two HPV vaccines since 2006, Gardasil™ in 2006 and Cervarix™ in 2007, new data regarding each of the vaccines' biological potency and safety were announced at competing pace and pitch.
2) Many questions have been raised namely:
   a. Are the vaccines effective and safe?
   b. What is cross-protection and how important is it?
   c. Should there be any age limit?
   d. Will they stay effective with time?
   e. Is one better than the other or would any one be?
3) Because some of the answers to these questions have been conflicting, as such we have become unclear about the similarities and differences of the two vaccines, sometimes to the point of confusion.
4) This article endeavours to present the data and current understanding of the HPV vaccines in a consolidated manner and hopes to clarify some 'conflicting' issues or understand the basis of their existence in the first place.

WHAT HAS HAPPENED SO FAR ?

1) Before 2002 : Clinicians have hardly heard about HPV Vaccines.
2) 2002 – 2005 : We started to hear about HPV vaccines being trialed.
3) 2006 – 2007 : HPV Vaccines trials were successful and the vaccines were launched worldwide, with extensive education of clinicians and users.
4) 2007 – 2009 : Competing new data were released for both the HPV vaccines. There were controversies, claims and counter-claims. But meanwhile, the use of both Vaccines spread.
5) 2010 : We are now seeing consolidation of data and starting to hear about new indications and new vaccines being trialed.

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HPV VACCINES TRIALS

There have been many clinical trials on the HPV vaccines and the key trials may be summarized below:

Gardasil™	Cervarix™
Proof of Principle Study (HPV 16 vaccine)	
FUTURE I (Phase II, 9-23)	Protocol 001/007 (Efficacy, 9-25)
FUTURE II (Phase III, 9-26)	PATRICIA TRIAL 008 (Efficacy, 9-25)
FUTURE III (Phase III, Adult Women)	Protocol 012, 014 (Immunobridging)
Protocol 019 (Male)	Protocol 013
Adolescent Immunogenicity	Protocol 015 (Efficacy, >25 Adult Women)
Sentinel Cohort – Nordic Registries	Protocol 010 (Head-to-Head)

A CHRONOLOGICAL PERSPECTIVE – KEY TO CLEAR UNDERSTANDING OF THE DATA

The best way to understand the similar and different properties of the 2 vaccines is to appreciate their development over the years.

Before 2002 – The 'Laboratory' Years

- There was increasing recognition of the role of HPV causing cervical cancers. In 1995 and then in 1999, HPV was found to be an essential causal factor in cervical carcinogenesis.
- Extensive amount of research on HPV vaccines were underway. HPV Virus-Like-Particles were synthesized as surrogates of HPV viral antigens. Laboratory and animal studies were performed culminating in human trials in the latter years of the '90s and early 2000s.

Year 2002 – The Proof-of-Principle Study

- In 2002, the FIRST clinical trial proving that a HPV vaccine (MSD : HPV-16 VLP) is effective in preventing persistent infection and high grade pre-cancers of the cervix (CIN-2+) was published, generating an enormous amount of excitement for the researchers, vaccines' companies, clinicians and users of the vaccines.

Years 2002 – 2006 : Trials and Launches

- Both the bivalent vaccine Cervarix (HPV-16 & 18) and the quadrivalent vaccine Gardasil (HPV-16 & 18 + HPV-6 & 11) underwent major Phase II and Phase III Efficacy and Safety trials.
- Because the results of the trials for both vaccines showed excellent outcomes, studies were concluded earlier than planned to permit women in the placebo group to benefit from them and for public use.
- These successful trials culminated in the launch of Gardasil (HPV-16 & 18 + HPV-6 & 11) in 2006 and then Cervarix (HPV-16 & 18) in 2007.

Years 2006 – 2007 : Efficacy and Safety Reports

- From the trials, the HPV vaccines Efficacy Reports were released and may be summarized to-date as follows:
  - Both vaccines were found to be Highly Effective with > 95% efficacy in women who were Tested to be NOT infected with HPV Vaccine-types at the time of Vaccination.
  - Both vaccines are effective against all endpoints from persistent infection to CIN2+.
  - They Do Not clear Existing HPV Infection.
  - They Do Not slow the Progression of CIN.
  - Realistically, protection would not be expected to be 100%, but certainly close to.

- Likewise, the respective Safety Reports were released and may be summarized as follows:
  - They are very safe vaccines to-date.
  - The Injection Site symptoms (pain, redness, swelling) are more frequent.
  - Systemic AEs are comparable with the Control Group.
  - Pregnancy Safety Outcome are comparable with the Control Group.
  - The recent Adverse Reports in the media are experienced during mass vaccinations and have NOT been shown to be causally related.
  - The Global Advisory Committee on Vaccine Safety referred to them as Safe Vaccines.
  - But Prudence should continue to be exercised and Continued Vigilance is Important.

Years 2007 – 2008 : Cross-Protection & Extended Protection

Cross-Protection

1) Data has consistently shown that there is Cross-protection Protection beyond vaccine HPV-types 16, 18 against other related High-Oncogenic Risk HPVs like HPV-31 & 45.
2) Such Cross-protection against High-Oncogenic Risk HPVs is Real. The question is "what is the degree and extent of cross-protection?"
3) But we need to be mindful that protection against HPV 16 & 18 is the Central Action contributing to the main impact of vaccination.
4) And that Cross-Protection is only an Added advantage contributing to a smaller added Impact in vaccination.

Extended Protection

1) There is now new data to show that women who have been previously infected (as indicated by their sero-positive status) but has cleared themselves of the HPV DNA from the cervico-vaginal epithelium (as indicated by their DNA-negative status), appears to be protected in the longer term as well when they are vaccinated.
2) This is an interesting finding as it would mean that previously infected but currently DNA-negative women can benefit from vaccination.

Women's Age is not a contra-indicating factor

1) Therefore, the suitability of HPV vaccination for a woman is not a question of her age but one of previous exposures and active infection.
2) It is true that Immunological Response better in younger women.
3) But Older women can also mount an immune response and can be protected.
4) In clinical practice, adult women form a very accessible population for HPV vaccination as they are financially independent and are direct decision makers.

Years : 2008 – 2009 : Current Controversy

1) In recent times, the factor of Antibodies Titres have generated a significant amount of interest as to whether protection against HPV infection occurs at a "Threshold Antibodies Level" or is it the "the Higher the level, the Better the protection."
2) This controversy is still unresolved.
3) What the recent Immunological Response Head-to-Head Trial Report has shown is that Cervarix generates a stronger immunological response than Gardasil in at the first 18 months following vaccination.
4) It was proposed that higher Antibodies Titres in the cervicovaginal mucous is critical for the protection of the cervix against HPV infections. And therefore, as Cervarix generates a stronger immunological response, protection may possibly be better.
5) On the other hand, Gardasil has shown High Efficacy Rate for Skin Warts Protection, which occurs in dry

skin, and hence highlighting that protection may involve immunological mechanisms beyond shear antibodies titres in mucosal secretions.

6) There is no direct comparative data to support one vaccine is more effective than the other to-date.

What is Needed?

The controversial claims and counterclaims by the respective vaccines have hence induced the urgent need for the study of the following:

1) Have we fully understood how HPV vaccines protect one against HPV infections?
2) What about the Role of Cell-Mediated Protection in HPV vaccination?
3) Comparable Efficacy Data would still be necessary to confirm a superior clinical potency.

Years 2009 – 2010 : Consolidation of Results

In the current year, we would expect to see the following:

1) Adult Women Trials data (Gardasil trial : concluded) (Cervarix : on-going)
2) Sustained Immunogenicity (Head-to-Head Trial) data (GSK HPV-010)
3) Safety Reports
4) More Indications (Gardasil – Male vaccination & Reducing Total HPV Disease Burden Beyond Cervical Cancers).

THE FUTURE

In the medium term, we look forward to:

1) Long-Term Efficacy data.
2) New Polyvalent HPV Vaccines.

LEARNING POINTS

- **The High Efficacy and Safety reports of both Gardasil and Cervarix should compel us to vaccinate and protect women.**
- **Age is not the limit – but 'active' infection is.**
- **The Cross-Protection issue will settle with the introduction of new polyvalent vaccines.**
- **Cervarix AS04 potentiates immuno-response – but the effect on Efficacy is pending.**
- **The Durability and Length of protection remains unclear but this should not hamper implementation programs.**
- **We should regularly consolidate and understand the current issues of HPV vaccines.**