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# Editorial

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With the guidance and blessings of Dr Aniruddha D Joshi and in association with Shree Aniruddha Upasana foundation we have great pleasure in presenting you this issue.

As with the earlier issues, we have tried to present various articles of common interest to empower the common man.

We start this issue with an article on plantar fasciitis. This is a very common ailment in general population causing pain and disability and this article explains the patho-mechanism of this condition and its management. The incidence of cervical cancer is increasing alarmingly and in the earlier issues we have covered it in detail. There is a lot of interest shown in its prevention and HPV vaccine is one of the many ways in which we can curb the rise of cervical cancer. We have included an article, which is the latest update on HPV vaccine. We have had a detailed article on this Vaccine in earlier issue and also an update in subsequent issue. This is a second update on the HPV vaccine.

In this issue we have an interesting case report of a Radicular cyst in Maxilla and its management is very well and lucidly explained.

We end this issue with the current hot topic all over the world and that is about Zika virus. The article explains the outbreak of this virus and its consequences.

Hope the readers enjoy reading the articles and gain knowledge so that the patients are benefited.

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# Plantar Fasciitis (Heel Pain)

- **Dr. Pradeep Moonot**

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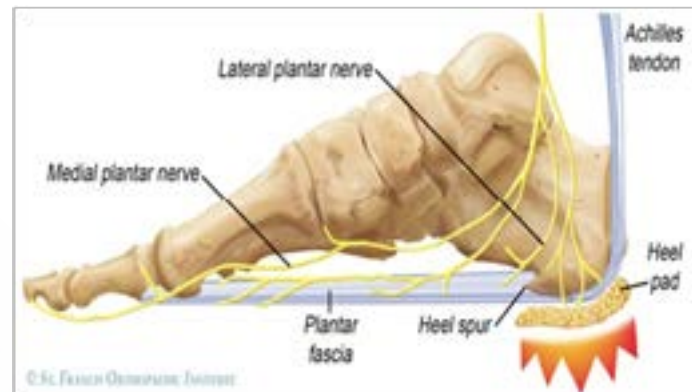
## The Injury

Plantar Fasciitis (heel-spur syndrome) is a common problem. It starts as a dull intermittent pain in the heel which may progress to a sharp persistent pain. Classically, it is worse in the morning with the first few steps, after sitting, after standing or walking, and at the beginning of sporting activity.

The plantar fascia is a thick fibrous material on the bottom of the foot. It is attached to the heel bone (calcaneus), fans forward towards the toe, and acts like a bowstring to maintain the arch in the foot.

A problem may occur when part of this inflexible fascia is repeatedly placed under tension, as in running. Tension causes an overload that produces an inflammation usually at the point where the fascia is attached to the heel bone. The result is pain. Plantar fascia injury may also occur at midsole or near the toes. Since it is difficult to rest the foot, the problem gradually becomes worse because the condition is aggravated with every step.

The inflammatory reaction at the heel bone may produce spike-like projections of new bone called heel-spurs. They are sometimes shown on X-rays. The exact relationship between heel spurs and plantar fasciitis is poorly understood. The heel spurs do not cause the heel pain and they are not the initial cause of the problem. Indeed some people may have heel spurs found incidentally on X-rays but may be completely pain free.



## Treatment

Improvement may take longer than expected, especially if the condition has been present for a long time. During recovery, loss of excess weight, good shoes and sedentary activities all help the injury to heal. You should return to full activity gradually.

- **Rest** : Use pain as your guide. If your foot is too painful, rest it.
- **Ice** : Ice the sore area for 30-60 minutes several times a day to reduce the inflammation. Apply a plastic bag of crushed ice over a towel. You should also ice the sore area for 15 minutes after activity.
- **Medication** : If your condition has developed recently, anti-inflammatory/analgesic medication (in tablet form), coupled with heel pads may be all that is necessary to relieve pain and reduce inflammation. If no pain relief has occurred after two or three months, however, an injection of either cortisone and/or local anaesthetic directly into the tender area may be considered.
- **Physiotherapy** : The initial objective of physiotherapy (when needed) is to decrease the inflammation. Later, the small

muscles of the foot can be strengthened to support the weakened plantar fascia.

- **Heel Pads** : A heel pad of felt, sponge or a newer synthetic material can help to spread, equalize and absorb the shock as your heel lands, thus easing the pressure on the plantar fascia.
- **Shoes** : Poorly fitting shoes can cause plantar fasciitis. The best type of shoe to wear is a good running shoe (jogger/trainer) with excellent support. The shoe that fits best should be chosen. Experiment with your athletic shoes to find a pair that is comfortable and gives you fewer symptoms.
- **Orthoses** : Orthoses are shoe inserts that Dr Pradeep Moonot may prescribe if necessary.
- **Taping** : Taping your foot to maintain the arch may benefit some people as this can take some of the pressure off the plantar fascia.
- **Night Splints** : These are plastic splints that keep the foot stretched and the ankle at right-angles when you are asleep. This maintains the tension in the plantar fascia and may help to alleviate some early morning symptoms during the first few steps of the day.
- **Surgery** : Surgery is rarely required for plantar fasciitis. It would be considered treatment if the pain is still incapacitating after at least 12 months of treatment. When needed, surgery involves release of the plantar fascia and release of a small nerve.

## Sports

Plantar fascia can be aggravated by all weight bearing sports. Any sport where the foot lands repeatedly, such as jogging or running can aggravate the problem. To maintain cardiovascular fitness, weight bearing sports can be temporarily replaced by non weight bearing sports (like swimming, cycling). Weight training can be used to maintain leg strength. When recovering from plantar fasciitis, return to sports activities slowly. If you have a lot of pain either during the activity or the following morning, you are doing too much.

## Exercise

- **Stretches** : Stand at arms' length from a counter or table with your back knee locked and your front knee bent. Slowly lean towards the table, pressing forward until a moderate stretch is felt in the calf muscles of your straight leg. Hold 10 seconds. Keeping both your heels on the floor, bend the knee of your straight leg until a moderate stretch is felt in your Achilles tendon. (Tendons attach muscles to bones; the Achilles tendon attaches the muscles of the calf to the heel bone). Hold 10 seconds. You should feel a moderate pull in your muscles and tendon, but no pain. Change legs and stretch the other leg. Repeat 10 times, 3 times a day.

# Human Papilloma Virus (HPV) Vaccine Update

- **Dr. Sharmila Pimple**

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## Human Papilloma Virus (HPV) Vaccines

Two prophylactic HPV Vaccine like Particle (VLP) vaccines, Gardasil R (Merck & Co NJ USA), a quadrivalent vaccine containing VLPs of types 6,11, 16 and 18, and Cervarix R (GlaxoSmithKline Biologicals, Belgium), a bivalent vaccine containing VLPs of types 16 and 18 are approved and have been licensed in over 100 countries since 2006 and have been introduced into national immunization programs in at least 58 countries with variable uptake. A vaccine targeting HPV 16/18 potentially prevents the majority of invasive cervical (66.2%) annually .

Bivalent, quadrivalent and nonavalent Vaccine containing HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 all are presently given prophylactically via three doses in a "prime-prime-boost" schedule ( 0, 2 and 6) over a 6-month period.

<b>Available HPV vaccines</b>			
	<b>Bivalent 2vHPV (Cervarix)</b>	<b>Quadrivalent 4vHPV (Gardasil)</b>	<b>9-valent 9vHPV (Gardasil 9)</b>
<b>L1 VLP types</b>	16, 18	6, 11, 16, 18	6, 11, 16, 18, <b>31, 33, 45, 52, 58</b>
<b>Manufacturer</b>	GlaxoSmithKline	Merck	Merck
<b>Adjuvant</b>	<b>AS04:</b> 500 µg aluminum hydroxide 50 µg 3-O-desacyl-4'- manophospheryl lipid A	<b>AAHS:</b> 225 µg amorphous aluminum hydroxyphosphate sulfate	<b>AAHS:</b> 500 µg amorphous aluminum hydroxyphosphate sulfate

L1, Major capsid protein; VLP, virus like particle

<http://www.cdc.gov/cancer/hpv/statistics/cases.htm>

The multicentre vaccine trials for the bivalent and quadrivalent vaccines included more than 20 000 women aged 15–26 years from more than ten countries in four continents.

Two main trials of the Quadrivalent vaccine : FUTURE I and FUTURE II trials.

Two main trials for the Bivalent vaccine: PATRICIA and the Costa Rica vaccine trial.

The primary endpoint in the phase III trials, and the basis for licensure in females for both vaccines, was demonstrating decrease in the Incident HPV 16- and 18-related CIN2/3 or AIS (CIN2+). These endpoints served as a surrogate marker for cervical cancer. [2,3]

### **Mechanisms of Vaccine-Induced Protection**

The current assumption is that HPV virus-like particle (VLP) vaccines protect via antibody.

Systemic immunization with L1 VLPs generates antibody concentrations 1–4 folds higher than in a natural infection, possibly because of high antigen concentration and delivery route that grants access to lymph nodes and spleen.

### **Vaccine Efficacy :**

Both bivalent and quadrivalent vaccines demonstrated remarkably high and similar efficacy and are able to prevent up to 90–100% of new HPV 16 and 18 infections and associated high grade CIN.

Quadrivalent vaccine also demonstrated strong protection against Genital Warts and vulvar/vaginal neoplasia associated with the vaccine types. CervarixR protected against vaccine-targeted anal infections in women in an end of study evaluation. The vaccines had no therapeutic effects against established infection or CIN.

### **Duration of Protection :**

For the prediction of the long-term duration of immunity, immunogenicity data is most crucial. High and sustained immunogenicity levels 9.4 years post-vaccination for bivalent vaccine were observed for each type in the vaccine. Immunogenicity for 9 years post-vaccination was also observed in the quadrivalent

vaccine. All vaccinees remained seropositive to HPV-16/18, with antibody titers remaining several folds above natural infection levels. There were no safety concerns.

Thus protection against Infection & Cervical pre cancers associated with HPV16/18 has been demonstrated for at least 9 years for both vaccines. The need for a booster dose will have to be assessed once more long-term data on efficacy against cervical cancer becomes available.

### **Vaccine Safety :**

Safety evaluations are important and communication about vaccine safety is critical. Events temporally associated with vaccination can be falsely attributed to vaccination.

### **Pre-licensure safety**

Pre-licensure safety evaluations conducted found no differences between vaccine and control groups for any Serious adverse events, New onset autoimmune and chronic diseases or Deaths between vaccine and control groups.

### **Post-licensure Safety**

WHO's Global Advisory Committee on Vaccine Safety (GACVS Report ) has reviewed data on HPV vaccine three times, for recent >175 million doses till March, 2014 for Post-licensure Safety evaluation. These reviews continue to confirm the safety of HPV vaccines. No increase in risk of autoimmune diseases, including Multiple Sclerosis, was observed among HPV vaccine recipients compared to those who have not received the vaccine.

### **Cross Protection against other HPV types :**

Partial cross-protection against phylogenetically related non-vaccine HPV types were also observed in both the vaccines. Bivalent vaccine showed protection for high grade cervical precancer or worse lesions for following other HPV vaccine types viz HPV 31 (88%), HPV 33 (68%), HPV 45 (82%), HPV 51 (54%) reported in the HPV naive cohort.

However protection for high grade cervical precancer or worse lesions was observed for only HPV 31 (70%) and not for any other HPV type for

the quadrivalent vaccine. [12]

### **Fewer than three dos:**

Costs and infrastructure complexities associated with a three-dose HPV vaccine programme had prompted further studies to test efficacy and immunogenicity of one and two-dose schedules of the HPV-16/18 vaccine. Study findings of one and two-dose schedules of the HPV-16/18 have now demonstrated immunological non-inferiority and protection against cervical HPV-16/18 infections, similar to the protection provided by the three-dose schedule.[13,14] HPV 16 antibody concentrations remained 24 times higher in the two-dose vaccine group and 9 times higher in the one-dose vaccine group compared with natural infection. Antibody concentrations after one dose remained stable over 4 years.

Two doses given 6 months apart also provided partial protection against HPV-31/33/45, similar to that reported for 3 doses.[17,18] WHO position paper on HPV vaccines, 2014 now recommends the use of a two-dose schedule of either vaccine for girls younger than 15 years. [18] All the above findings have strong ramifications on aiding plans for national introductions in LMICs.

### **Nonvalent Vaccine**

Nonavalent Vaccine containing HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, a prophylactic vaccine approved by the Food and Drug Administration (FDA) for use in females aged 9 through 26 years and males aged 9 through 15 years in December 2014. In February 2015 Advisory Committee on Immunization Practices (ACIP) recommended 9-valent human papillomavirus (HPV) vaccine (9vHPV) (Gardasil 9, Merck and Co., Inc.) as one of three HPV vaccines that can be used for routine vaccination.[19]

Nonavalent vaccine was tested for efficacy analyzing more than 14 000 women aged 16–26 years have shown non inferior immunogenicity of the immune response to HPV 6, 11, 16, and 18 compared with the quadrivalent vaccine. Efficacy against a composite endpoint of HPV 31, 33, 45, 52, and 58 high-grade cervical, vulvar, and vaginal lesions was 96•7% (95% CI 80•9–99•8). Concomitant Use with other vaccines was safe with no impact on Immunogenicity. [20]

The bivalent, quadrivalent and nonavalent vaccines all protect against HPV 16 and 18, types that cause about 66% of cervical cancers, 9vHPV targets five additional cancer causing types, which account for about 15% of cervical cancers. [21]

### **Co-administration of HPV with other vaccines**

Co-administration of HPV with other vaccines is another measure that can simplify vaccine delivery logistics for the already overstrained health care delivery operations in LMICs.

Systematic review of safety and immunogenicity of HPV vaccines coadministered with other vaccines included meningococcal conjugate, hepatitis A, hepatitis B, combined hepatitis A and B, tetanus, diphtheria, pertussis, and inactivated poliovirus vaccines and have shown Noninferiority of immune response and an acceptable safety profile. Co-administration with vaccines that are routinely given to adolescents and those that have demonstrated safety and non inferior immune response, will not only facilitate vaccine delivery but also help reduce the number of clinic visits to achieve optimal coverage.

### **Conclusion**

The clinical trial results so far strongly support the potential of the vaccines for public health implementation to reduce the cervical cancer burden. [

WHO recommends routine HPV vaccination under national immunization programmes provided, vaccine introduction is programmatically feasible, sustainable financing can be secured and the cost-effectiveness of vaccination strategies in the country or region is considered.

Majority uptake for HPV vaccination in public health programs is primarily in high-resource countries which shares the least burden of cervical cancer. Introduction of HPV vaccines in LMIC shares the same concerns as in the implementation of cervix cancer screening programs in terms of the financial and logistic requirements along with concerns for participation of the targeted age group for adequate vaccine coverage to achieve the desirable lifetime reductions in cervical cancer risks. HPV vaccine coverage of 70% was predicted to yield 40-50%



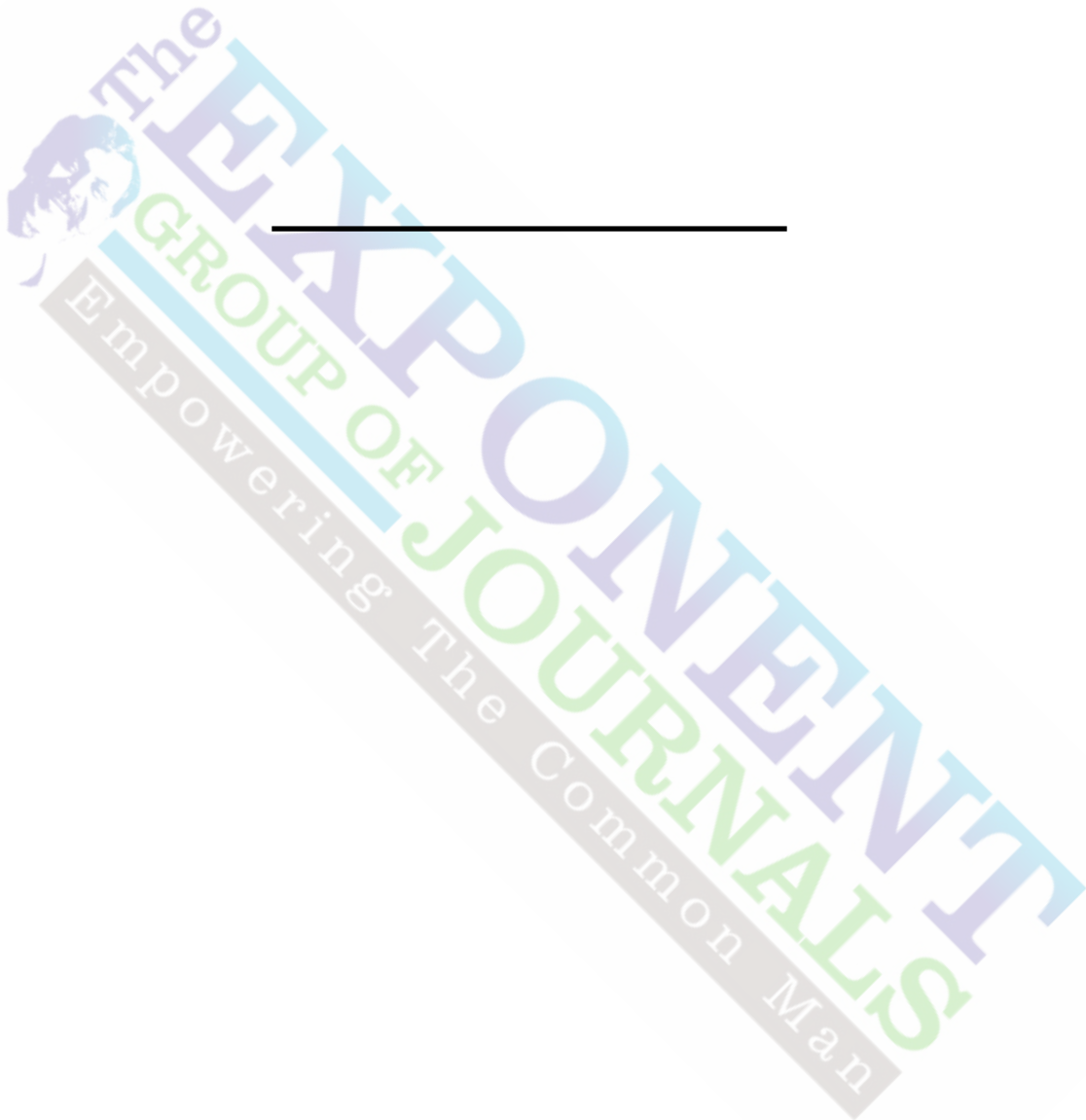
mean reduction in the lifetime risk of cancer. [4] Prohibitively high cost of the current vaccines, logistics for vaccine storage, transport, administration of injectable temperature sensitive vaccine, validation of appropriate platforms for vaccine delivery currently preclude the introduction of the HPV vaccines in Low Middle Income Countries (LMIC). Cost effective vaccine along with operationally feasible vaccine delivery logistics and strategies will help the LMICs with the highest burden of cervical cancer incidence and mortality to implement organized population based HPV vaccination programs in the countries where it is most needed.

**Conflicts of Interest : None**

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# Case Report: Radicular Cyst in Maxilla

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## ABSTRACT

Maxillofacial region is affected by a large number of cysts. These Odontogenic cysts can be developmental or inflammatory. Radicular cyst, also known as Periapical cyst, is an inflammatory cyst formed at the apex of the tooth. It is a true cyst as it is a pathologic cavity lined by epithelium and contains fluid or pus cells. The case presented here is of a Radicular cyst encountered in anterior maxilla. It was treated by Endodontic treatment of the involved teeth, followed by Surgical Enucleation of the cyst and apicectomy of the involved teeth.

## KEYNOTES

Radicular cyst, Periapical cyst, Root canal treatment, Surgical Enucleation, Maxilla

## INTRODUCTION

Radicular cysts are the most common cystic lesions affecting the human jaw, comprising about 52 to 68 % of all the cysts. The incidence is highest in the anterior maxilla as the maxillary incisors are most prone to caries, trauma, pulpal death due to developmental defects and irritating effects of synthetic restorative materials. The cyst forms as a sequel to the Periapical Granuloma. The etiology for a radicular cyst is long standing infection in the periapical zone. The cyst arises from the epithelial remnants, derived from the epithelial cell rests of Malassezin the Periodontal Ligament, stimulated to proliferate an existing periapical granuloma, by an inflammatory process originating from pulpal necrosis of a non-vital tooth.

The flow of events –

- Trauma / Caries
- Pulpitis
- Pulpal Necrosis

- Periapical Abscess
- Periapical Granuloma
- Periapical Cyst / Radicular cyst
- Bone loss due to expansion of cyst

## CASE STUDY

### • Chief Complaint

A 35 year old female patient reported to the dental clinic with the chief complaint of a fractured black tooth. No pain present. History of trauma to the anterior maxilla region 25 years back. She also reported some pus discharge 6 months back which had settled with a course of antibiotics.

### • Intra-oral examination

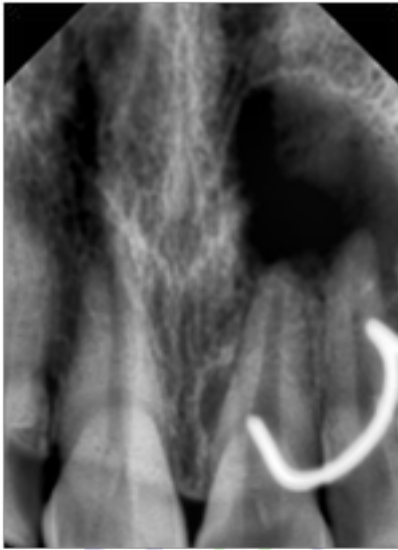
Ellis Class III fracture of tooth # 21.  
Slight tender to percussion teeth #21, #22  
Vitality test showed teeth #21, #22 non vital  
Sinus opening seen at the apex of tooth #22  
No expansion of labial or palatal cortical plates seen  
No relevant medical findings noted



Pre- op image

## Radiological findings

- Intra-oral Periapical Radiograph



Pre-op Radiograph

A 9mm x 8mm round well-defined, corticated, radiolucent lesion seen extending from the lamina dura of apices of teeth #21, #22.

- Cone Beam Computed Tomography (CBCT)

Localized, ovoid, periapical, osteolytic radiolucency is noted involving the apices of teeth #21, #22 with the left anterior maxilla. Defect involving dentin and pulp space is noted with the middle 3rd of the coronal portion of #21. Wider pulp canal space noted with #21 as compared with #11. The periapical lesion shows fairly defined, corticated and partially sclerotic margins. Labiopalatal expansion is noted with #21, #22. The lesion shows thinning and sclerosis of the labial cortical plate. Discontinuity in the cortical lining of the labial cortical plate is noted along the midroot level in relation to the mesial aspect of #21 and along the apical 3rd region of #22. Probable discontinuity is noted with the palatal cortical plate in relation to teeth #22, #23. The lesion shows close approximation to the nasopalatine canal medially and the anterior nasal floor superiorly. Discontinuity is noted involving the apices of #21, #22. The lesion appears to involve the lamina dura along the mesial aspect of the radicular portion of #23. The approximate maximum dimensions of the lesion are 12.7mm superoinferiorly, 13.7mm labiopalatally and 16mm mesiodistally. Mucosal thickening is noted within the right and left maxillary sinus.

- Differential Diagnosis

1. Radicular / Periapical Cyst
2. Benign Odontogenic Cyst
3. Keratocystic Odontogenic tumour

- Treatment Plan

1. ENDODONTIC PHASE – Root Canal treatment of teeth #21, #22, #23
2. SURGICAL PHASE – Cyst Enucleation + Apicectomy of teeth #21, #22, #23
3. PROSTHETIC PHASE – Crowns for teeth #21, #22, #23

## ENDODONTIC PHASE



Post Root Canal Treatment Radiograph

Root Canal Treatment was started for teeth #21, #22, #23. 3 sittings were taken to finish the treatment. On the first sitting, initial biomechanical preparation was completed. #21, #22 were completely necrotic, while #23 was partially necrotic. #21 had a blunder canal. No purulent discharge was noted. Calcium hydroxide dressing was used as an intra-canal medicament. After the canals were absolutely dry, obturation was done for all three teeth.

## SURGICAL PHASE



**Immediate Post Surgery image**

After local anesthesia, crevicular incision was made with releasing incision. A full thickness mucoperiosteal flap was raised. Trephination of the buccal cortical plate was done to expose the cyst. Turbid white contents were found within the cavity. A thorough enucleation and curettage was carried out to avoid any remnants of the cyst. Lavage with sterile saline was done. The contents of the cyst were stored in 10% formalin and sent for histopathological examination. The apicectomy of teeth #21, #22, #23 was done followed by retrograde filling with Mineral Trioxide Aggregate (MTA). The flap was repositioned back and sutured. Patient was informed about the post-operative care. The sutures were removed after 7 days.

## PROSTHETIC PHASE



**Tooth preparation for crowns #21,#22,#23**



**Final Cementation of crowns**

After 2 weeks, the prosthetic phase began. The gingival healing was fair. Keeping in mind the esthetic demand, E-Max crowns were done for teeth #21, #22, #23. A night guard was also delivered to the patient.

### • Histopathological findings

**Intraosseous specimen Gross anatomy:** Multiple soft tissue bits of cystic sac received, aggregating to approximately 1 cm, soft in consistency, irregular shape, brownish in colour.

**H & E stained slide:** Cystic lumen and cystic capsule with lining epithelium present at places. Epithelium is stratified squamous epithelium type with proliferation in an arcading forking pattern. Capsule is fibrocellular, with areas of moderate chronic inflammatory cell infiltrate, chiefly lymphocytes and plasma cells, areas of foamy macrophages noted. Spicules of lamellar bone, hemorrhagic areas, necrotic debris present

### • Final Diagnosis

### **RADICULAR / PERIAPICAL CYST**

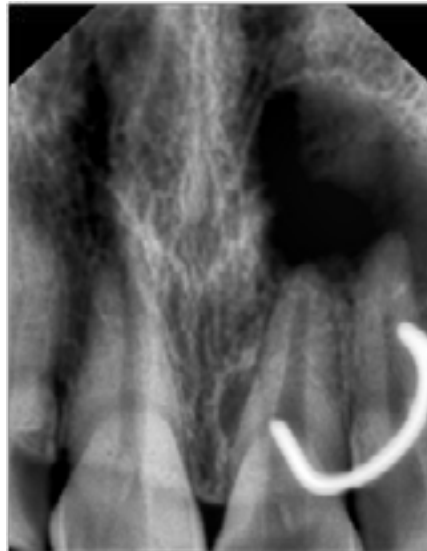
### **DISCUSSION**

Pathogenesis of radicular cysts has been described as comprising of three distinct phases: the phase of initiation, the phase of formation and the phase of enlargement. Radicular cysts are usually asymptomatic and are left unnoticed, until detected by routine radiographic examination where as some long standing cases may undergo an acute exacerbation of the cystic lesion and develops signs

and symptoms such as swelling, tooth mobility. Associated teeth are always non-vital and may show discoloration. It clinically exhibits as buccal or palatal swelling. At first, the enlargement is bony hard but as the cyst increases in size, bony covering becomes very thin and the swelling exhibits springiness and becomes fluctuant when the cyst has completely eroded the bone. Treatment options for radicular cysts can be conventional nonsurgical endodontic treatment when lesion is localized or surgical treatment like enucleation, marsupialization or decompression when the lesion is large.

## CONCLUSION

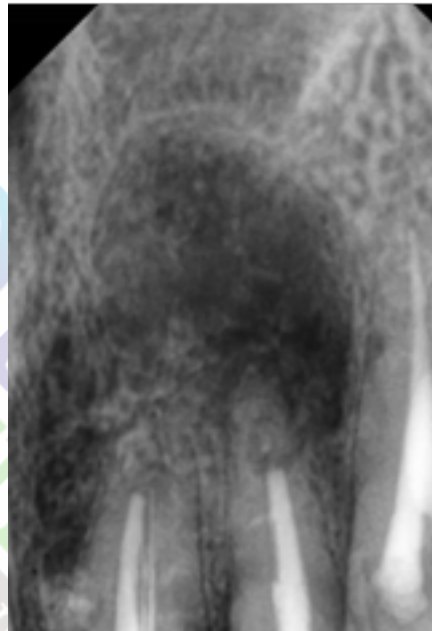
Radicular cyst is a severe outcome of a neglected trauma that happens in early childhood. Parents must be made aware of this seriousness. Dentists must also evaluate the case. If the patient is asymptomatic, regular follow up with radiological investigation is necessary. Early intervention will definitely have more predictable results.



Pre-op Radiograph



Pre-op smile



3 weeks post-op radiograph showing trabecular pattern in the cavity



Post- op smile

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# ZIKA: Another menace of the mosquito brigade

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## Abstract:

While the world is getting closer to controlling the Ebola epidemic – a disease that has caused havoc in some African countries, reports of another emerging illness from South America, has made the world take notice. Previously limited to sporadic cases in Africa and Asia, the emergence of Zika virus in Brazil in 2015 heralded rapid spread throughout the Americas. Its striking link with microcephaly in babies born to mothers infected early during the course of their pregnancy, has alarmed the public health and disease control agencies throughout the world. Zika virus disease is caused by a virus transmitted by *Aedes aegypti* mosquito. People with Zika virus disease usually have symptoms that can include mild fever, skin rashes, conjunctivitis, muscle and joint pain, malaise or headache. These symptoms normally last for 2-7 days. There is no specific treatment or vaccine currently available. This article attempts to study the situation so far and highlight some important issues relevant to this crisis.

**Keywords:** Zika, microcephaly, epidemic, Zika and contraception, Pyriproxifen

## Introduction

Zika virus is an emerging mosquito-borne virus that was first identified in Uganda in 1947 in rhesus monkeys through a monitoring network of sylvatic yellow fever<sup>1</sup>. It is named after the Zika forest in Uganda<sup>2</sup>. It was subsequently identified in humans in 1952 in Uganda and the United Republic of Tanzania. Since the 1950s, Zika virus disease has been known to occur within a narrow equatorial belt from Africa to Asia. The virus spread eastward across the Pacific Ocean. Since 2013–2014, Zika virus outbreaks have been reported in Oceania to French Polynesia, New Caledonia, the Cook Islands and Easter Island and in 2015 to Mexico, Central America, the Caribbean and South America where the Zika outbreak has reached pandemic level

## Epidemiology

**Agent factors** : Zika virus is a single stranded RNA virus.

**Genre** : Flavivirus (includes several other mosquito-borne viruses of clinical importance e.g. dengue virus, West Nile virus and yellow fever virus)

**Vector** : *Aedes* mosquitoes (which usually bite during the morning and late afternoon/evening hours)

**Reservoir** : Unknown

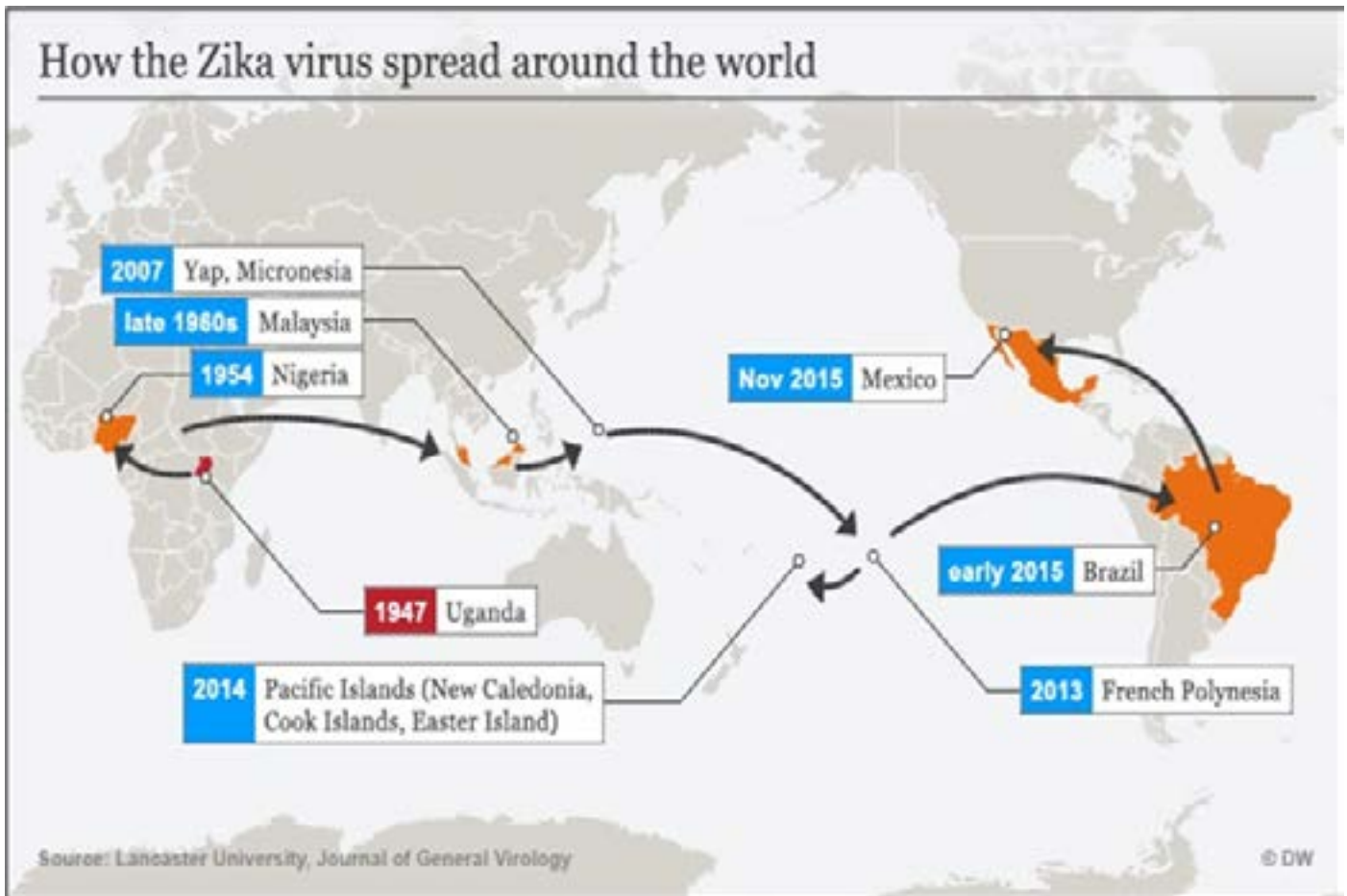


Figure 1: Origin and spread of Zika virus around the world

### Geographical distribution:

Serosurveillance studies in humans suggest that Zika virus is widespread throughout Africa, Asia, and Oceania. However, these studies may overestimate the virus's true prevalence, given serologic overlap between Zika virus and related flaviviruses, such as dengue virus (DENV) and West Nile virus (WNV)<sup>3</sup>.

Historically, symptomatic Zika virus infections were limited to sporadic cases or small clusters of patients. This pattern changed in 2007, when the first major outbreak of Zika virus infection occurred in Yap (Federated States of Micronesia), where  $\approx 73\%$  of the population were infected and symptomatic disease developed in  $\approx 18\%$  of infected persons. Since then, Zika virus infection has spread rapidly. Outbreaks have occurred in French Polynesia, Cook Islands, Easter Island, New Caledonia, and most recently, the Americas with sporadic exportations to Europe.

Zika virus was first reported in May 2015 in continental South America in Brazil, where  $\approx 440,000$ – $1,300,000$  persons have subsequently been infected (as of February 16, 2016). Furthermore, 29 other countries in the Americas have reported autochthonous Zika virus transmission, including Puerto Rico and US Virgin Islands. Except for 2 sexually acquired cases, Zika virus in the United States, Canada, and Europe has been restricted to travelers from affected areas; a patient who delivered an infant with microcephaly in Hawaii had spent part of her pregnancy in Brazil.

As of 1st May 2016, 20 countries or territories have reported local transmission of the virus and as many as 1.3 million persons have been affected in Brazil alone. Figure 2: Countries and territories with Active Zika virus transmission.



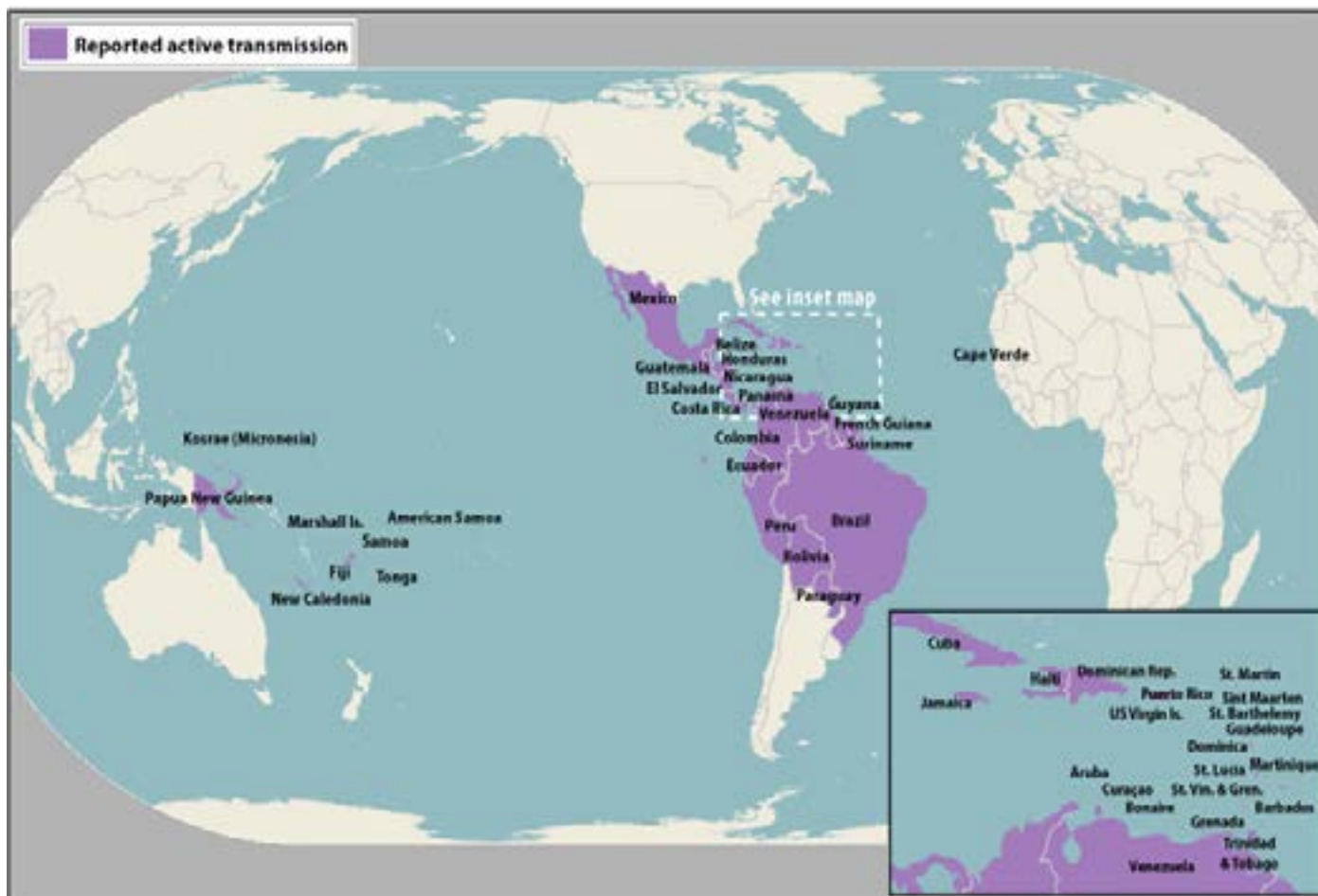


Figure 2: Countries and territories with Active Zika virus transmission

Transmission:

**1. Through mosquito bites:**

- Zika virus is transmitted to people primarily through the bite of an infected *Aedes* species mosquito (*A. aegypti* and *A. albopictus*). These are the same mosquitoes that spread dengue and chikungunya viruses.
- These mosquitoes typically lay eggs in and near standing water in things like buckets, bowls, animal dishes, flower pots and vases. They prefer to bite people, and live indoors and outdoors near people.
- Mosquitoes that spread chikungunya, dengue and Zika are aggressive daytime biters. They can also bite at night. Mosquitoes become infected when they feed on a person already infected with the virus. Infected mosquitoes can then spread the virus to other people through bites.



Fig 2: *Aedes aegypti* mosquito: vector for Zika virus. Note white bands on legs and body.

**2. From mother to child:** A pregnant woman can pass Zika virus to her fetus during pregnancy.

To date, there are no reports of infants getting Zika virus through breastfeeding. Because of the benefits of breastfeeding, mothers are encouraged to breastfeed even in areas where Zika virus is found.

**3. Through sexual contact:**

Zika virus can be spread by a man to his sex partners. In known cases of sexual transmission, the men developed Zika virus symptoms. From these cases, we know the virus can be spread when the man has symptoms, before symptoms start and after symptoms resolve. In one case, the virus was spread a few days before symptoms developed.

The virus is present in semen longer than in blood.

**4. Through blood transfusion**

There have been multiple reports of blood transfusion transmission cases in Brazil. These reports are currently being investigated.

During the French Polynesian outbreak, 2.8% of blood donors tested positive for Zika and in previous outbreaks, the virus has been found in blood donors.

### Clinical Manifestations

In humans, the incubation period from mosquito bite to symptom onset is ~3–12 days. Infection is likely to be asymptomatic in ~80% of cases. All ages are susceptible (4 days–76 years). When symptoms occur, they are typically mild, self-limiting and nonspecific. Similarity to other arbovirus infections (dengue and chikungunya virus) may confound the diagnosis.

Commonly reported symptoms include rash, fever, arthralgia, myalgia, fatigue, headache, and conjunctivitis. Rash, a prominent feature is maculopapular and pruritic in most cases; it begins proximally and spreads to the extremities with spontaneous resolution within 1–4 days of onset. Fever is typically low grade (37.4°C –38.0°C). Symptoms resolve within 2 weeks; accounts of longer persistence are rare.

Once a person has been infected, he or she is likely to be protected from future infections.

### Diagnosis

Clinical evaluation alone is unreliable for a diagnosis of Zika virus infection. Because of clinical overlap with other arboviruses, diagnosis relies on laboratory testing. Evaluation for Zika virus, chikungunya and dengue should be undertaken concurrently for all patients who have acute fever, rash, myalgia, or arthralgia after recent (previous 2 weeks) travel to an area of ongoing Zika virus transmission.

RT-PCR on serum samples remains the most specific diagnostic approach and is the preferred testing method for Zika virus during the acute phase of illness (<7 days from symptom onset).

### Management and Prevention

No specific treatment or vaccine is available for Zika virus infection. Management is supportive and includes rest, fluids, antipyretics and analgesics. Aspirin and other nonsteroidal anti-inflammatory drugs should be avoided until dengue is excluded because of the risk for hemorrhage among dengue patients.

Other general measures focus on prevention of mosquito bites, including individual protection (e.g., long pants, light-colored clothing, insect repellents, bed nets), particularly during known *Ae. aegypti* peak biting times (early morning and late afternoon). Community-level strategies target mosquito breeding through elimination of potential egg-laying sites (e.g. potted plant saucers, water storage units, used tires) by drying wet environments or using insecticide treatment. Insect repellents containing ingredients such as DEET, picaridin and IR3535 are safe for use during pregnancy when used in accordance with the product label.

Pregnant women residing in countries that are not Zika virus–endemic are advised against travel to affected countries. Testing should be offered to all pregnant women who have traveled to areas with ongoing Zika virus transmission. Serial fetal ultrasounds should be considered to monitor fetal anatomy and growth every 3–4 weeks in pregnant women with positive or inconclusive Zika virus test results and the infant should be tested at birth. Men who reside in or have traveled to an area of active Zika virus transmission and who have a pregnant partner should abstain from sexual activity or use condoms during sex; similar guidelines apply for men with a

nonpregnant female sex partner who is concerned about sexual transmission of Zika virus.

### **Certain issues worth considering:**

#### **Zika virus and Birth defects – Reviewing the evidence for causality**

A recent study published in the New England Journal of Medicine reviews the evidence for causality between Zika virus and birth defects. Excerpts from the article:

To determine whether Zika virus infection during pregnancy causes these adverse outcomes, the authors evaluated available data using criteria that have been proposed for the assessment of potential teratogens.

Two approaches have been used to identify potential teratogens (exposures to a mother during pregnancy that have a harmful effect on her embryo or fetus): first, the identification of a combination of a rare exposure and a rare defect (sometimes referred to as the astute clinician approach), and second, the use of epidemiologic data to confirm an association. In 1994, Thomas Shepard, a pioneer in the field of teratology, proposed a set of seven criteria for “proof” of human teratogenicity that incorporated both approaches.

The first criterion states that a proven exposure to an agent must occur at a critical time during prenatal development. The severe microcephaly and other brain anomalies that have been observed in many infants are consistent with an infection occurring in the first or early second trimester of pregnancy. Several case reports and studies have shown that women who had fetuses or infants with congenital brain anomalies that were believed, on the basis of the mother’s symptoms or laboratory confirmation, to be due to Zika virus infection were infected in the first or early second trimester of pregnancy, as determined either according to the timing of the symptoms or according to the timing of travel to an area where Zika virus is endemic.

An analysis of the timing of laboratory-confirmed Zika virus transmission in certain states in Brazil and of the increase in the cases of microcephaly identified the first trimester as the critical time period for infection. Thus, Shepard’s first criterion (for establishing teratogenicity causality) has been

met.

Shepard’s second criterion requires that two epidemiologic studies of high quality support the association. Although ecologic data do not necessarily qualify as an epidemiologic study, data from Brazil regarding the temporal and geographic association between Zika virus infection and the later appearance of infants with congenital microcephaly are compelling.

Two epidemiologic studies also provide support. In a study conducted during the outbreak in Brazil<sup>8</sup>, 88 pregnant women who had had an onset of rash in the previous 5 days were tested for Zika virus RNA. Among the 72 women who had positive tests, 42 underwent prenatal ultrasonography, and fetal abnormalities were observed in 12 (29%); none of the 16 women with negative tests had fetal abnormalities. The abnormalities that were observed on ultrasonography varied widely, and some findings lacked postnatal confirmation because the pregnancies were ongoing.

A retrospective analysis after the 2013–2014 outbreak of Zika virus disease in French Polynesia identified eight cases of microcephaly; the authors used serologic and statistical data and mathematical modeling to estimate that 1% of the fetuses and neonates who were born to mothers who had been infected with Zika virus in the first trimester had microcephaly — a prevalence that was approximately 50 times as high as the estimated baseline prevalence. However, this estimate was based on small numbers, confidence intervals were wide, and the risk of other adverse outcomes (e.g., other brain anomalies) was not assessed. Although these studies provide important evidence in support of a causal relationship between Zika virus and microcephaly and other brain anomalies, both have limitations as noted by their authors, such as a lack of control for confounding factors and relatively small numbers of cases, and therefore they do not meet the stringent criteria set by Shepard.

In conclusion the authors comment: we suggest that sufficient evidence has accumulated to infer a causal relationship between prenatal Zikavirus infection and microcephaly and other severe brain anomalies. Also supportive of a causal relationship is the absence of an alternative explanation; despite the extensive consideration of possible causes,

researchers have been unable to identify alternative hypotheses that could explain the increase in cases of microcephaly that were observed first in Brazil and then retrospectively in French Polynesia, and now in preliminary reports that are being investigated in Colombia.

Moving from a hypothesis that Zika virus is linked to certain adverse outcomes to a statement that Zika virus is a cause of certain adverse outcomes allows for direct communications regarding risk, both in clinical care settings and in public health guidance, and an intensified focus on prevention efforts, such as the implementation of vector control, the identification of improved diagnostic methods, and the development of a Zika virus vaccine.

### **Controversies surrounding Zika outbreak**

Debate over Safe and Legal Abortion in Latin America  
Zika has fuelled another controversy in South America – most of the countries in this continent do not have liberal abortion laws. “Don’t get pregnant” – say the official guidelines from Brazil, Colombia and Honduras. El Salvador has gone so far as to recommend women do not get pregnant until 2018. However, most of the Latin American countries are also Catholic, so access to birth control is often poor and abortion is flat-out banned. This kind of recommendation that women should avoid pregnancy is not realistic against the background of very tough abortion laws and lack of access to essential reproductive and sexual health services.

### **Pyriproxifenand not Zika– cause for microcephaly?**

A group of Argentine physicians has challenged the notion that Zika virus leads to microcephaly. According to the Physicians in Crop-Sprayed Towns (PCST), a chemical larvicide, Pyriproxifen that produces malformations in mosquitoes was injected into Brazil's water supplies in 2014 in order to stop the development of mosquito larvae in drinking water tanks. It was used in a massive government-run program tasked to control the mosquito population in the country. Pyriproxifen is a larvicide manufactured by Sumitomo Chemical, a company associated [PDF] with Monsanto. However, PCST has referred to Sumitomo as a subsidiary of Monsanto. For instance, the Brazilian Health Ministry had injected pyriproxifen to reservoirs in the state of Pernambuco. This area has a very high proliferation

of *Aedes aegypti* mosquito. Pernambuco is also the first state in Brazil to notice the problem. The state contains 35 percent of the total microcephaly cases in the country. While there is no solid proof yet that the larvicide causes microcephaly, the local government of Grande do Sul, in the southern portion of Brazil suspended the use of the chemical larvicide pyriproxifen.

However, Pyriproxifen has been approved and registered for use in the past 20 years by the authorities of around 40 countries around the world and despite long term and widespread use in many different settings no correlation with microcephaly has been reported."

### **Genetically Modified Mosquitoes**

Biotech firm Oxitec has created a genetically modified breed of *Aedes aegypti* mosquito<sup>11</sup>. The GMO mosquito (OX513A) carries a gene that causes offspring to die before they reach reproductive age. Oxitec did a controlled test in Piracicaba, Brazil, which cut the mosquito population by 82% in a few months, prompting the city to contract with Oxitec and allow it to build a mosquito-making factory there.

The offspring die before maturity because they develop serious birth defects (irony alert – babies of mothers with the virus are also born with the rare birth defect microcephaly). Oxitec used the same GMO mosquitoes last year in areas of Brazil to control the spread of dengue fever – the same general areas where the birth defects caused by the Zika virus in Brazil are now concentrated.

Coincidence? Reports show that 3-4% of the offspring of GMO mosquitoes don't die prematurely and instead survive to adulthood where they can reproduce and potentially pass their survivalist genes caused by the modifications to their offspring. Those offspring already in Brazil can potentially mate with the new Zika GMO mosquitoes and possibly spawn generations of adults that can continue to spread Zika.

### **Viewpoint...**

The world has witnessed numerous pandemics and near-pandemic like situations warranting immediate efforts from local, national and international disease control agencies. Swine flu, avian influenza, SARS, Ebola, now Zika and we don't know what else will

follow. But a critical aspect of all these epidemics/pandemics is that the most vulnerable sections in any society, are the most affected.

While medical science has made tremendous progress in diagnostics and therapeutics, the millennium development goals can only be achieved when basic needs like hygiene, sanitation, safe and potable drinking water and appropriate waste disposal are provided to all communities. Zika has highlighted a very important issue of reproductive and sexual health services for women in South America. Health is multi-factorial and it is time for inter-sectoral co-ordination and all stakeholders to come together in this regard.

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