Chikungunya

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course
Acknowledgments

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Viral Diseases Branch, WRAIR
AUG 2015
Disclaimer

The views expressed in this presentation are those of the speaker and authors, and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.
Chikungunya: Introduction

• Single Stranded RNA Virus
  – Genus *Alphavirus*, Family *Togaviridae*
  – Related to Ross River, O’nyong-nyong viruses
• Transmitted by *Aedes aegypti* and *A. albopitus*
• Single serotype, multiple genotypes
• Large outbreaks, high attack rates
• Fever and polyarthralgia
• Arthralgia is painful and debilitating.
Transmission: Vectors

- **Aedes aegypti**
  - Urban areas of tropics and subtropics
  - Prefers humans for bloodmeal
  - Flowerpots, trash, cups
  - Will bite another if feeding is interpreted

- **Aedes albopictus**
  - Asian tiger mosquito
  - Bites more hosts vs. *Ae.aegypti*
  - Wider distribution vs. *Ae.aegypti*
    - Found in temperate climates
  - Dengue / CHIK co-infection documented
Transmission: Other Considerations

- CHIKV mutations may enhance transmission
  - Depends on local vector and climate
  - Reunion Island, mutation A226V enhanced transmission by *Ae.albopictus*

- Time and season of travel important when considering likelihood of an outbreak on a non-endemic area

- CHIKV’s extrinsic incubation time = approx. 10 days.

- *Aedes* mosquitoes live 2 weeks to month
  - longer in warmer climates

- Warmer temperature decreases extrinsic incubation time
Transmission: Other Methods

• Rare But Documented
  – Intrapartum from mother to child
  – In \textit{uterus} transmission resulting in miscarriage
  – Percutaneous needlestick
  – Laboratory exposure

• Theoretical: Blood transfusion, Organ Transplantation

• No Evidence of Breast Milk Transmission
Global Distribution of CHIKV

http://www.cdc.gov/chikungunya/map/index.html

Countries and territories where chikungunya cases have been reported*
(as of March 10, 2015)

*Does not include countries or territories where only imported cases have been documented. This map is updated weekly if there are new countries or territories that report local chikungunya virus transmission.
Epidemiology

• Endemic in West Africa
  – Human, mosquitoes, primates, ? Other animals

• Spread by travelers in unexposed populations
  – High attack rate

• Outbreaks followed by years of little activity

• Indian Ocean and Asia (2004-2010)
  – Reunion Island: 34% of population
  – Comoro Islands: 63% had positive antibodies
  – India: 1.4 million cases of 2006

Spread to Malaysia, Thailand, Singapore, China
http://127.0.0.1:8081/plosntds/article?id=info:doi/10.1371/journal.pntd.0002921
Americas – AFHSC (DOD), 22 APR 2015
Since DEC 2013

- 1,365,626 suspected, probably or confirmed cases
  - 190 deaths attributed
  - Limited reporting
- US
  - 2,558 in 47 states and DC
  - Florida
    - 11 local cases in 2014
  - Puerto Rico and USVI
    - 4513 cases in 2014
2,792 cases from US states (11 locally transmitted)
4,702 from all US territories
Up to July 7, 2015: 207 cases from 32 states, 94 cases from US territories
* Most Caribbean cases: May – Nov. (rainy season)
U.S. DoD – AFHSC Data

• As of 7 APR, the DoD has reported 65 locally acquired, lab-confirmed chikungunya cases at Fort Buchanan, Puerto Rico among active duty (AD), National Guard, Reserve and other personnel since 28 JUL 2014.

• As of 31 MAR, DoD reports 31 deployment- or travel-related, lab-confirmed chikungunya cases.

• Among deployed personnel, five cases have been reported from Curacao.

• Absence of diagnostic code presents challenge
CHIK Clinical Features

• Reported 72% - 97% symptomatic
  – Seroprevalence studies shows variability
  – Genotype variation
• Incubation 3-7 days (range 1-12 days)
• FEVER
• POLYARTHRALGIA
  – Symmetrical, peripheral (smaller joints)
    • ankles, toes, fingers, elbows, wrists, knees
  – Painful and debilitating
  – May persist months to years
Other Clinical Manifestations

- Headache
- Maculopapular rash
- Myalgia
- Arthritis
- Conjunctivitis
- Nausea/Vomiting
## CHIK Clinical Features

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Frequency range (% of symptomatic patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>76–100</td>
</tr>
<tr>
<td>Polyarthralgias</td>
<td>71–100</td>
</tr>
<tr>
<td>Headache</td>
<td>17–74</td>
</tr>
<tr>
<td>Myalgias</td>
<td>46–72</td>
</tr>
<tr>
<td>Back pain</td>
<td>34–50</td>
</tr>
<tr>
<td>Nausea</td>
<td>50–69</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4–59</td>
</tr>
<tr>
<td>Rash</td>
<td>28–77</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>12–32</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3–56</td>
</tr>
</tbody>
</table>

*Table compiled from a number of different studies.*[^1]
Laboratory Findings

• Lymphopenia
• Thrombocytopenia
• Elevated Creatinine
• Elevated Hepatic Transaminases
Clinical Presentation

Figure 4: Typical rashes with chikungunya virus infection
Maculopapular rash, petechial spots and erythroderma of arms (A), legs (B), and feet (C).

Lancet 2012; 379: 662-71
OCID course 2015
Rash
CHIK Clinical Features

(a) 
(b) 

http://vir.sgmjournals.org

A. M. Powers and C. H. Logue

OCID course 2015
Figure 3: Severe manifestations of chikungunya in an infant

Hyperalgesic infant aged 7 months with maculopapular rash presented with oedema of hands and feet. Other presentations include swollen ankles or wrists, without typical inflammatory joints.
Atypical CHIK Manifestations

- Cranial nerve palsies
- Guillain-Barre syndrome
- Meningoencephalitis
- Retinitis
- Uveitis
- Myelitis
- Myocarditis
- Hepatitis
- Nephritis
- Hemorrhage
- Bullous skin lesions (in infants)
Disease Progression / Outcome

• Acute symptoms lasts 7-10 days
• Infants, elderly, co-morbid patients at higher risk for severe disease and death
• Persistence or relapse of joint symptoms variable depending on location and population
  – Polyarthritis
  – Raynaud’s syndrome
Persistent Arthralgia Associated with Chikungunya Virus: A Study of 88 Adult Patients on Reunion Island

Gianandrea Borgherini,1 Patrice Poubleau,1 Annie Jossaume,1 Arnaud Gouix,1 Liliane Cotte,2 Alain Michault,3 Claude Arvin-Berod,1 and Fabrice Paganin1

1Service de Pneumologie et Maladies Infectieuses, 2Centre d'Investigation Clinique, and 3Laboratoire de Virologie, Groupe Hospitalier Sud Reunion, Saint Pierre, La Réunion, France

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous pain</td>
<td>31 (55.4)</td>
</tr>
<tr>
<td>Intermittent pain</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>25 (45.6)</td>
</tr>
<tr>
<td>At least once per week</td>
<td>12/25 (48)</td>
</tr>
<tr>
<td>At least once per month</td>
<td>10/25 (40)</td>
</tr>
<tr>
<td>Not specified</td>
<td>3/25 (12)</td>
</tr>
<tr>
<td>Experienced relapse</td>
<td>12 (21.4)</td>
</tr>
<tr>
<td>Mean no. of relapses per patient ± SD</td>
<td>1.5 ± 1.2</td>
</tr>
<tr>
<td>Period between acute chikungunya and first relapse, mean months ± SD</td>
<td>8 ± 5.4</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>40 (71.4)</td>
</tr>
<tr>
<td>Discomfort in everyday activities</td>
<td>26 (46.4)</td>
</tr>
<tr>
<td>Symmetrical joint pain</td>
<td>36 (64.3)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) or proportion (%) of patients, unless otherwise indicated.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Self-reported pain</th>
<th>Pain on physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean no. of involved joints ± SD</td>
<td>6.2 ± 4.2</td>
<td>3 ± 3.8</td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metacarpophalangeal joints</td>
<td>32 (57.1)</td>
<td>15 (26.8)</td>
</tr>
<tr>
<td>Metatarsal joints</td>
<td>27 (48.2)</td>
<td>15 (26.8)</td>
</tr>
<tr>
<td>Wrist</td>
<td>28 (50)</td>
<td>9 (16.1)</td>
</tr>
<tr>
<td>Ankle</td>
<td>26 (46.4)</td>
<td>16 (28.6)</td>
</tr>
<tr>
<td>Elbow</td>
<td>13 (23.2)</td>
<td>8 (14.3)</td>
</tr>
<tr>
<td>Shoulder</td>
<td>25 (44.6)</td>
<td>17 (30.4)</td>
</tr>
<tr>
<td>Knee</td>
<td>32 (57.1)</td>
<td>12 (21.4)</td>
</tr>
<tr>
<td>Rachis</td>
<td>13 (23.2)</td>
<td>7 (12.5)</td>
</tr>
<tr>
<td>Sternoclavicular joints</td>
<td>1 (1.8)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Hip</td>
<td>10 (17.9)</td>
<td>3 (5.4)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated.

Clinical Infectious Diseases 2008:47:469–75
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1058-4838/2008/4704-0005$15.00
DOI: 10.1098/590003

OCID course 2015
Persistent Chikungunya

Three clinical components, singly / in combination:

1. Distal polyarthritis / monoarthritis improved with NSAIDs;
2. Frequent tenosynovitides in the hands, wrists, or ankles, sometimes responsible for carpal or tarsal tunnel syndromes, highly sensitive to short-term systemic corticotherapy; and
3. Exacerbation of pain in previously injured joints and bones requiring painkillers.

Persistent Chikungunya
Persistent Chikungunya

Calcifications in shoulder tendon 18 months after infection

Inflammatory osteoarthritis, foot, 5 years after infection
Pathogenesis

- **Theories**
  - Viral persistence in tissue sanctuaries
  - Evasion of immune responses
  - Re-activation of virus
  - Uncontrolled proinflammatory cytokine response
  - Cross-reactivity with self-antigens

- **Immunopathology**
  - Strong innate responses
    - Antiviral IFN-α
    - Pro-inflammatory cytokines, chemokines, growth factors
  - Followed by activation of adaptive immunity
    - Activation and proliferation of CD8+ T cells (early)
    - Switch to CD4+ T-cell response (late)
Diagnosis

Criteria

1 Clinical criteria:
Acute onset of fever >38.5°C and severe arthralgia or arthritis

2 Epidemiological criteria:
Residing in or visited epidemic area within 15 days before onset of symptoms

3 Laboratory criteria:
After acute phase
- virus isolation
- presence of viral RNA
- specific IgM antibodies
- four-fold increase in IgG titres in paired samples

Definition

Possible case when not explained by other medical condition: dengue or alphaviral infection, arthritic disease, endemic malaria

Probable case if clinical and epidemiological criteria are met: other pathogens with similar clinical manifestations can co-circulate within the same geographical region

Confirmed case if a patient tests positive for one of the laboratory criteria, irrespective of clinical manifestations
Testing Methods

• Culture for virus in BSL 3 lab
• RT-PCR for viral RNA
• Serology for IgM and neutralizing antibodies
• Seroconversion or 4X rise in titers
  – PRNT, HI, or ELISA titer
• Immunohistochemical staining
Viral Culture yield = 3 or fewer days from illness onset

Table 6. Typical results of samples tested at various time points post-infection.

<table>
<thead>
<tr>
<th>Days post illness onset</th>
<th>Virus testing</th>
<th>Antibody testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1-3</td>
<td>RT-PCR = Positive</td>
<td>IgM = Negative</td>
</tr>
<tr>
<td></td>
<td>Isolation = Positive</td>
<td>PRNT = Negative</td>
</tr>
<tr>
<td>Day 4-8</td>
<td>RT-PCR = Positive</td>
<td>IgM = Positive</td>
</tr>
<tr>
<td></td>
<td>Isolation = Negative</td>
<td>PRNT = Negative</td>
</tr>
<tr>
<td>&gt;Day 8</td>
<td>RT-PCR = Negative</td>
<td>IgM = Positive</td>
</tr>
<tr>
<td></td>
<td>Isolation = Negative</td>
<td>PRNT = Positive</td>
</tr>
</tbody>
</table>
Available Tests

• Antibody assays
  – Many available, none approved by U.S. FDA
  – Some approved to use in Europe
  – Euroimmun and Inbios products performed best in CDC studies comparing 9 assays
  – Others performed inconsistently or poorly

• RT-PCR methodology not standardized

• Testing at CDC, state health departments, and commercial laboratories

• Testing available at WRAIR VDB
### CHIK vs. Dengue

<table>
<thead>
<tr>
<th>Clinical and laboratory features</th>
<th>Chikungunya virus infection</th>
<th>Dengue virus infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;102°F or 39°C)</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Myalgias</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Arthalgias</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Headache</td>
<td>++</td>
<td>++&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rash</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Bleeding dyscrasias</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Elevated hematocrit</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean frequency of symptoms from studies where the two diseases were directly compared among patient seeking care; ++ = 70-100% of patients; +++ = 40-69%; + = 10-39%; +/- = <10%; - = 0%<sup>32,33</sup>

<sup>b</sup> Often retroorbital

Table modified from Staples et al.<sup>34</sup>

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*Figure 1. Affected joints (in black) in a patient with CHIKV polyarthritis presenting 6 weeks after onset of illness.*

Chikungunya viral polyarthritis.
Raj J Carmona, Saeed Shaikh and Nader A Khalidi
J Rheumatol 2008;35:935-936
# Chikungunya: A Potentially Emerging Epidemic?

Michelle M. Thiboutot kak1,2, Senthil Kannan2, Omkar U. Kawalekar2, Devon J. Shedlock2, Amir S. Khan3, Gopalsamy Sarangan4, Padma Srikanth4, David B. Weiner2, Karuppiyah Muthumani2*

Table 1. Comparison of clinical features of Chikungunya and Dengue virus.

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Chikungunya Virus (CHIKV)</th>
<th>Dengue Virus (DENV)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Fever, asthenia</td>
<td>Common</td>
<td>Common</td>
<td>[6,8]</td>
</tr>
<tr>
<td>2) Myalgia</td>
<td>Possible</td>
<td>Very common</td>
<td>[6]</td>
</tr>
<tr>
<td>3) Polyarthrosis</td>
<td>Very Common, edematous</td>
<td>None</td>
<td>[56]</td>
</tr>
<tr>
<td>4) Tenosynovitis</td>
<td>Yes</td>
<td>None</td>
<td>[57]</td>
</tr>
<tr>
<td>5) Leukopenia</td>
<td>None</td>
<td>Yes</td>
<td>[58]</td>
</tr>
<tr>
<td>6) Thrombocytopenia</td>
<td>None</td>
<td>Yes</td>
<td>[59]</td>
</tr>
<tr>
<td>7) Rash</td>
<td>Days 1–4, important skin edema</td>
<td>Days 3–7</td>
<td>[6,35,58]</td>
</tr>
<tr>
<td>8) Retro-orbital pain</td>
<td>Rare</td>
<td>Common</td>
<td>[60]</td>
</tr>
<tr>
<td>9) Hypotension</td>
<td>Possible</td>
<td>Common, Days 5–7</td>
<td>[60,61]</td>
</tr>
<tr>
<td>10) Minor bleeding</td>
<td>Chronic polyarthritis up to 1 year</td>
<td>Common</td>
<td>[17,56]</td>
</tr>
<tr>
<td>11) Second stage</td>
<td>Possible; Tenosynovitis at M2–M3 Raynauds syndrome at M2–M3</td>
<td>Fatigue up to 3 mo</td>
<td>[6,56,57,58,62,63]</td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pntd.0000623.t001
Other Differential Diagnosis

Chikungunya: Prominent arthralgia, acute high fever, diffuse rash, no respiratory symptoms

- Dengue – larger joints, low platelets
- Malaria – Intermittent fevers, anemia
- Enteric Fever – subacute, bradycardia, abdominal pain
- Leptospirosis – Conjunctival suffusion, jaundice, water
- Relapsing Fever – Intermittent fever, neck stiffness
- Ross River Virus - Australia
- Rubella – low grade fever, coryza, conjunctivitis
- Epstein-Barr Virus – pharyngitis, lymphadenopathy
- Meningococcal Infection – hemorrhagic rash, meningitis
Treatment

- No specific antiviral therapy; treatment is symptomatic
- Assess hemodynamic status and provide supportive care
- Evaluate for other serious conditions and treat appropriately
- Collect specimens for diagnostic testing
- Acetaminophen or paracetamol for initial fever and pain
- Consider using narcotics or NSAIDs
- If the patient may have dengue, do not use aspirin or other NSAIDs (e.g., ibuprofen, naproxen, toradol) until they have been afebrile ≥48 hours and have no warning signs for severe dengue
Novel Treatments?

Development of a Highly Protective Combination Monoclonal Antibody Therapy against Chikungunya Virus


Pankaj Pal¹, Kimberly A. Dowd², James D. Brien³, Melissa A. Edeling⁴, Sergey Gorlatov⁵, Syd Johnson⁵, Iris Lee³, Wataru Akahata⁶, Gary J. Nabel⁶, Mareike K. S. Richter⁷, Jolanda M. Smit⁷, Daved H. Fremont⁴,⁸, Theodore C. Pierson², Mark T. Heise⁹, Michael S. Diamond¹,³,⁸,*
Prevention

- Personal Protective Measures
- Avoidance
- Vector control
- Vaccine Development Challenges
  - Market share
  - Stigma of live virus vaccines
  - Demonstrating efficacy
  - Viral evolution
CHIKV Vaccine Candidates Past Phase 1

• Live Attenuated Chikungunya  
  – WRAIR / US Army  
  – Entered phase 2: funding and market interest lacking

• Virus-like particle vaccine (VRC 311)  
  – NIH

• Recombinant measles-virus-based vaccine  
  – Themis Bioscience  
  – WRAIR partnership
US Military contributions to the global response to pandemic chikungunya

Charles H. Hoke Jr. a,*, Judy Pace-Templeton a, Phillip Pittman b, Frank J. Malinoski b, Paul Gibbs b, Tracy Ulderich c, Michelle Mathers a, Beverly Fogtman b, Pamela Glass b, David W. Vaughn d

Code No. TSI-GSD 218

Chikungunya Vaccine, Live, Attenuated, Dried.

Store at -20 C or lower

CAUTION: NEW DRUG LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE.

THE SALK INSTITUTE
Government Services Division
P.O. Box 250
Swiftwater, PA 18370 U.S.A.

Chikungunya virus (CHIK 181/Clone 25), prepared in MRC-5 cell culture. After reconstitution, the vaccine contains less than 0.02 µg Neomycin base and 0.25g% human serum albumin U.S.P. per mL.

For reconstitution: Add 21 mL of Sterile Water for Injection, U.S.P.
Dose: 0.5 mL subcutaneously.
After reconstitution: Store at +4 C and use within 3 hours.

CAUTION: This vaccine vial contains live virus. Autoclave before discarding.
Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active-comparator, first-in-man trial


Findings Between Nov 22, 2013, and Feb 25, 2014, we randomly assigned 42 participants to receive the low dose (n=12), the medium dose (n=12), or the high dose (n=12) of the measles-virus-based candidate vaccine, or Priorix (n=6), of whom 36 participants (86%; n=9, n=12, n=10, n=5, respectively) were included in the per-protocol population. The candidate vaccine raised neutralising antibodies in all dose cohorts after one immunisation, with seroconversion rates of 44% (n=4) in the low-dose group, 92% (n=11) in the medium-dose group, and 90% (n=10) in the high-dose group. The immunogenicity of the candidate vaccine was not affected by pre-existing anti-measles immunity. The second vaccination resulted in a 100% seroconversion for all participants in the candidate vaccine groups. The candidate vaccine had an overall good safety profile, and the rate of adverse events increased with vaccine dose and volume. No vaccination-related serious adverse events were recorded.

Interpretation The live recombinant measles-virus-based chikungunya vaccine had good immunogenicity, even in the presence of anti-vector immunity, was safe, and had a generally acceptable tolerability profile. This vaccine is the first promising measles-virus-based candidate vaccine for use in human beings.
Findings 25 participants were enrolled from Dec 12, 2011, to March 22, 2012, into the three dosage groups: 10 μg (n=5), 20 μg (n=10), and 40 μg (n=10). The protocol was completed by all five participants at the 10 μg dose, all ten participants at the 20 μg dose, and eight of ten participants at the 40 μg dose; non-completions were for personal circumstances unrelated to adverse events. 73 vaccinations were administered. All injections were well tolerated, with no serious adverse events reported. Neutralising antibodies were detected in all dose groups after the second vaccination (geometric mean titres of the half maximum inhibitory concentration: 2688 in the 10 μg group, 1775 in the 20 μg group, and 7246 in the 40 μg group), and a significant boost occurred after the third vaccination in all dose groups (10 μg group p=0.0197, 20 μg group p<0.0001, and 40 μg group p<0.0001). 4 weeks after the third vaccination, the geometric mean titres of the half maximum inhibitory concentration were 8745 for the 10 μg group, 4525 for the 20 μg group, and 5390 for the 40 μg group.

Interpretation The chikungunya VLP vaccine was immunogenic, safe, and well tolerated. This study represents an important step in vaccine development to combat this rapidly emerging pathogen. Further studies should be done in a larger number of participants and in more diverse populations.
Summary

• Possible exposure + Prominent arthralgia, acute high fever, diffuse rash, no respiratory symptoms

• Incubation is less than 2 weeks, 3-7 days average

• Check for malaria, must rule out dengue

• No proven treatment, symptomatic management

• New outbreak may occur any time, vector throughout many part of the world

New therapies and vaccine development efforts ongoing
QUESTIONS?