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### Infectious Etiologies of Chronic Diseases

#### DEFINITION

- Sudden insult leaves permanent deficits (e.g., Polio)
- Outcome of infection predisposes to chronic sequelae (e.g., lung disease after pre-term birth)
- **Microbe causes chronic illness and disability through progressive pathology**

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### Infectious Etiologies of Chronic Diseases

#### EXAMPLE CAUSAL ASSOCIATIONS

1958	<i>Schistosoma</i> spp.	Bladder cancer
1964	Epstein-Barr virus	Burkitt's lymphoma
1975	Hepatitis B virus	Hepatocellular carcinoma
1984	<i>Helicobacter pylori</i>	Duodenal & gastric ulcers
1987	Human papillomavirus	Cervical cancer
1989	Hepatitis C virus	Chronic liver disease Hepatocellular carcinoma Mixed cryoglobulinemia
1989		
1990		
1991	KSHV/ human herpesvirus 8	Kaposi sarcoma
1992	<i>Tropheryma whippellii</i>	Whipple's disease

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<b>Infectious Etiologies of Chronic Diseases</b>
<b>SPECTRUM</b>
<ul style="list-style-type: none"> <li>➤ Syndromes &amp; Organ systems</li> </ul>


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<b>Infectious Etiologies of Chronic Diseases</b>
<b>SPECTRUM</b>
<ul style="list-style-type: none"> <li>➤ Syndromes &amp; Organ systems</li> <li>➤ Pathogens                   bacteria                                   parasites                                   prions                                   viruses</li> </ul>


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<b>Infectious Etiologies of Chronic Diseases</b>
<b>SPECTRUM</b>
<ul style="list-style-type: none"> <li>➤ Syndromes &amp; Organ systems</li> <li>➤ Pathogens                   bacteria                                   parasites                                   prions                                   viruses</li> <li>➤ Triggers &amp; outcomes    1 microbe <input checked="" type="checkbox"/> &gt;1 syndrome                                   &gt;1 microbe <input checked="" type="checkbox"/> 1 outcome</li> </ul>


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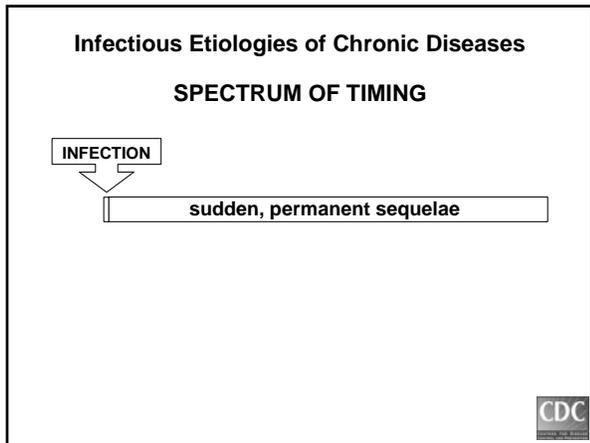
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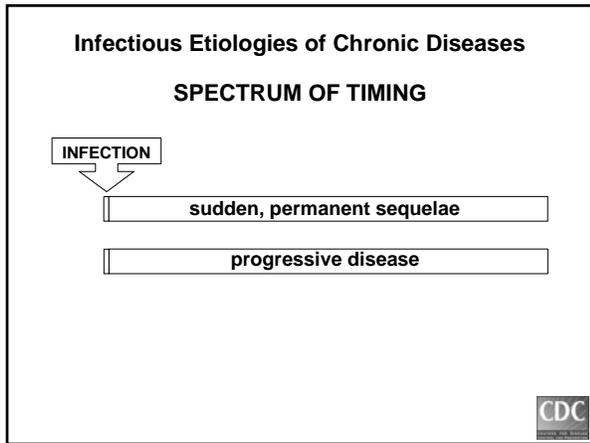
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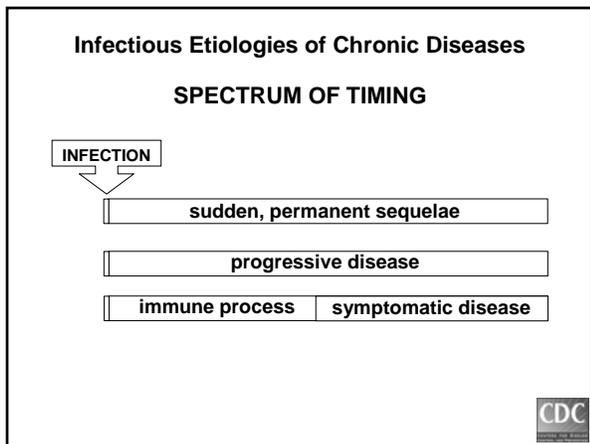
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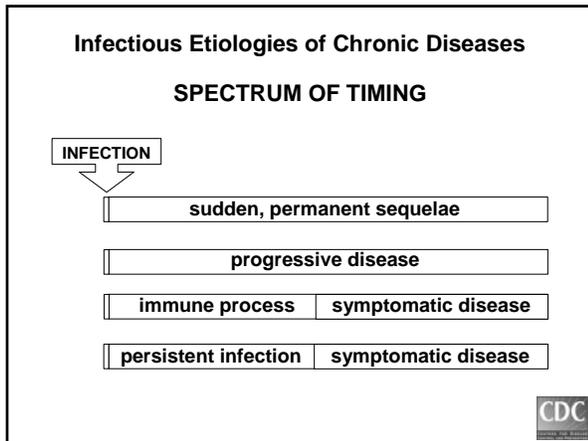
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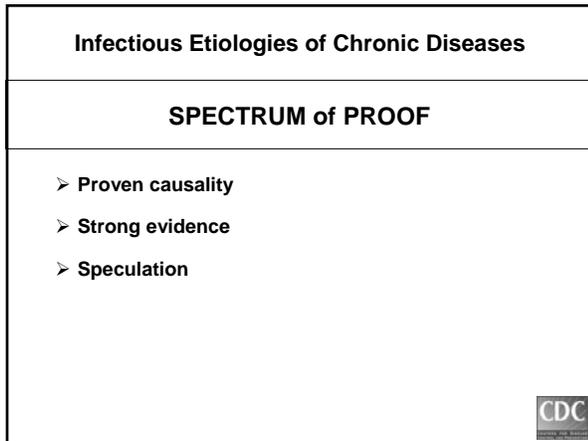
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**Infectious Etiologies of Chronic Diseases**

**Examples: WELL-RECOGNIZED ASSOCIATIONS**

*“Classics”*

Polio	Polio virus
Trachoma	<i>Chlamydia trachomatis</i>
Chagas cardiomyopathy	<i>Trypanosoma cruzi</i>

*Chronic Infection or Disease Process*

Cervical cancer	Human papillomavirus
CLD, Liver cancer	Hepatitis B and C viruses
Lyme arthritis	<i>Borrelia burgdorferi</i>
Peptic ulcer disease	<i>Helicobacter pylori</i>
Whipple’s disease	<i>Tropheryma whippelii</i>
Bladder cancer	<i>Schistosoma haematobium</i>

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**Infectious Etiologies of Chronic Diseases**

**Examples: ESTABLISHED or STRONG ASSOCIATIONS**

*Sequelae of Acute Event or Intra-partum Infection*  
 Hearing loss                      Cytomegalovirus (CMV)

*Chronic Infection or Disease Process*  
 Cryoglobulinemia              Hepatitis C virus  
 Gastric cancer                  *Helicobacter pylori*  
 Neuroborreliosis                *Borrelia burgdorferi*  
 Reactive arthritis                Enteric bacteria,  
    *Chlamydia trachomatis*  
 Uveitis, Retinitis                *Borrelia burgdorferi*  
    *Toxoplasma gondii*  
 Vasculitis                         HBV, HCV




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**Infectious Etiologies of Chronic Diseases**

**Examples: POTENTIAL to SPECULATIVE ASSOCIATIONS**

*Sequelae of Acute Event or Intra-partum Infection*  
 Atherothrombosis                *Chlamydia pneumoniae*, CMV  
 Pre-term birth sequelae (neurologic, pulmonary)      *Ureaplasma urealyticum*

*Chronic Infection or Disease Process*  
 Atherosclerosis                  *Chlamydia pneumoniae*  
 Diabetes mellitus                Enteroviruses/Coxsackie B virus  
 Inflammatory bowel disease      *Mycobacterium avium* subsp. *paratuberculosis*, *Yersinia*, luminal bacteria  
 Obsessive-compulsive disorders (PANDAS)      Group A *Streptococcus*  
 Lupus                                Epstein-Barr virus/Viruses




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**Infectious Etiologies of Chronic Diseases**

**CAUSAL**

*Helicobacter pylori* in Peptic Ulcer Disease

Analytic Tool	Strength Of Association
Tissue (ulcer) – histology	+ + + +
Human challenge	+ + + +
Culture	+ + +
PCR – strain identification	+ + + +
Virulence factors – Ab, PCR	+ +
Treatment trials	+ + + +
Urea breath test	+ + + (+)
Serology, stool antigen detection	+ + +
Animal models	+ +




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**Infectious Etiologies of Chronic Diseases**

**CAUSAL**

Hepatitis B virus in CLD, Liver Cancer

Analytic Tool	Strength Of Association
Epidemiology and time-space	+ + +
Serology – HBsAg (HBeAg, anti-HBc)	+ + + +
Serum viral assays	+ + (+)
Tissue – PCR, IHC	+ + + +
Vaccine & other prevention	+ + + +
Treatment trials	+ + +
Animal model	+ + +




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**Infectious Etiologies of Chronic Diseases**

**CAUSALITY NOT PROVEN**

*Chlamydia pneumoniae* in Atherosclerotic CVD

Analytic Tool	Strength Of Association
Serology	+ +
PCR on PBMC	+
Tissue (atheroma) – IHC, ICC	+ + (+)
Tissue (atheroma) – PCR	+ + (+)
Culture	+
Animal models	+ +
Treatment trials	+




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**Infectious Etiologies of Chronic Diseases**

**INFECTIOUS  
DISEASE**

**CHRONIC  
DISEASE**




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**Infectious Etiologies of Chronic Diseases  
PREVENTION OPPORTUNITY**

**90 million with Chronic Illness and Disability  
In the U.S.**



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**Infectious Etiologies of Chronic Diseases  
PREVENTION OPPORTUNITY**

**90 million with Chronic Illness and Disability**

suppose  
10%  
attributable to  
Infectious Diseases



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**Infectious Etiologies of Chronic Diseases  
PREVENTION OPPORTUNITY**

**90 million with Chronic Illness and Disability**

suppose  
10%  
attributable to  
Infectious Diseases

**Impact 9 million people in U.S.**



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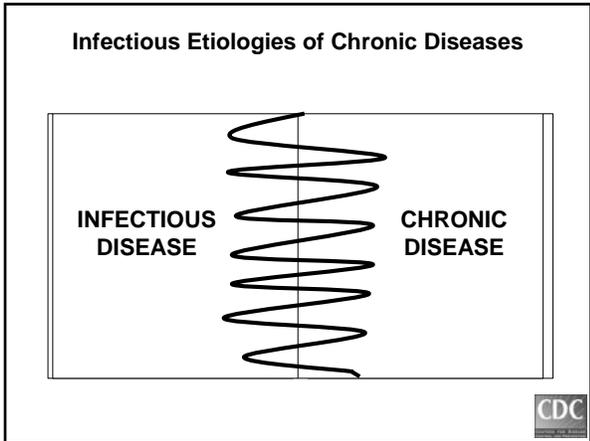
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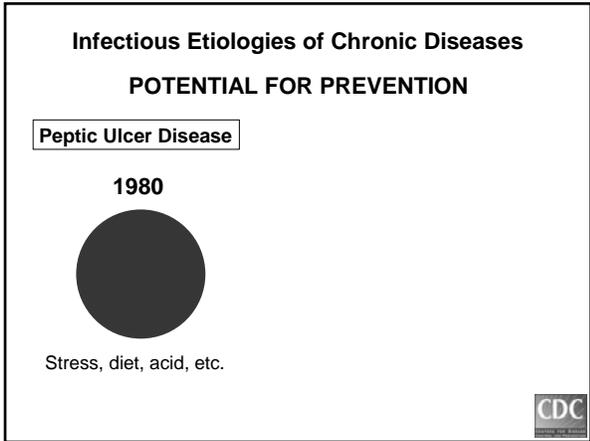
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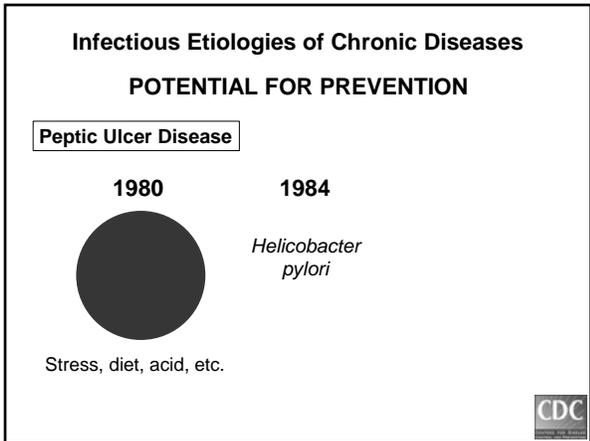
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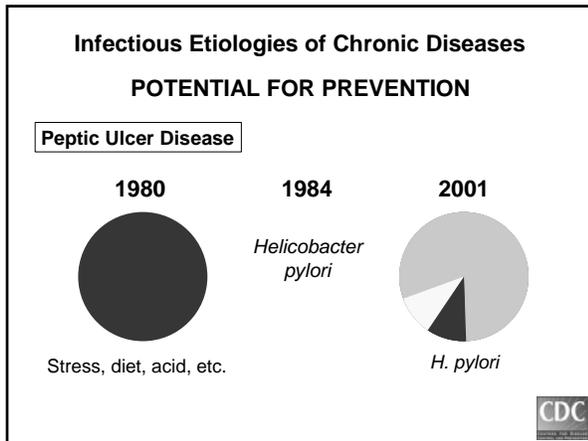
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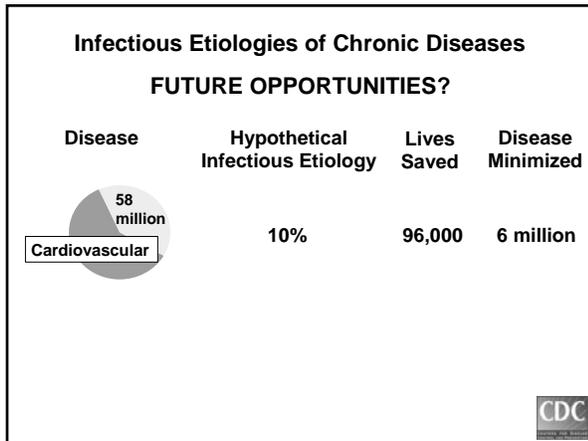
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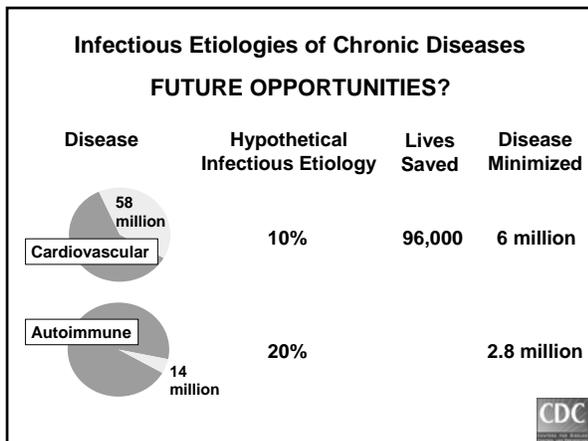
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**Infectious Etiologies of Chronic Diseases**

**HURDLES AND CHALLENGES**

- **Recognize associations early**
- **Detect causal agents**
- **Identify populations at risk for**
  - Infection
  - Chronic outcome
- **Determine pathogen-specific attributable fraction**
- **Assess long-term impact**
  - Disability prevalence
  - Microbe eradication, antimicrobial resistance



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**Infectious Etiologies of Chronic Diseases**

**TECHNICAL CHALLENGES**

- **Ubiquitous agents**
- **“New” and “old” microbes – new sites**
- **Multiple agents – ONE outcome**
- **ONE microbe – multiple outcomes**
- **Multifactorial disease**



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**Infectious Etiologies of Chronic Diseases**

**MORE TECHNICAL CHALLENGES**

- **Exposure-disease interval**  
(agent may have cleared)
- **Technology**
  - Culture methods (improved)
  - Sensitive and specific detection tools
  - Validated assays
  - Distinguishing active, latent & past infection



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**Infectious Etiologies of Chronic Diseases**

**EVALUATION CHALLENGES IN THE U.S.**

- **Heterogeneity of U.S. population**
  - Geographic diversity
  - Racial/ethnic diversity
- **Migration**
- **Changing epidemiology**
- **Diverse environmental exposures**



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**Infectious Etiologies of Chronic Diseases**

**PROGRESS REQUIREMENTS**

- **Uniform case definitions**
- **Networks of populations and laboratories**
- **Prospective collection and storage**
  - Appropriate specimens & appropriate collection
- **Careful interpretation of data**
  - Molecular detection ≠ causality
  - Common exposures ↗ high prevalence in all
  - IgG serology = a past exposure



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**Infectious Etiologies of Chronic Diseases**

**LABORATORY PROGRESS REQUIREMENTS**

- **Standardized, reproducible diagnostic tools**
- **Specific and sensitive assays, validated in tissues under study**
- **Validation against “gold standard”**
- **Assays that differentiate between past and current infection**
- **High throughput assays?**



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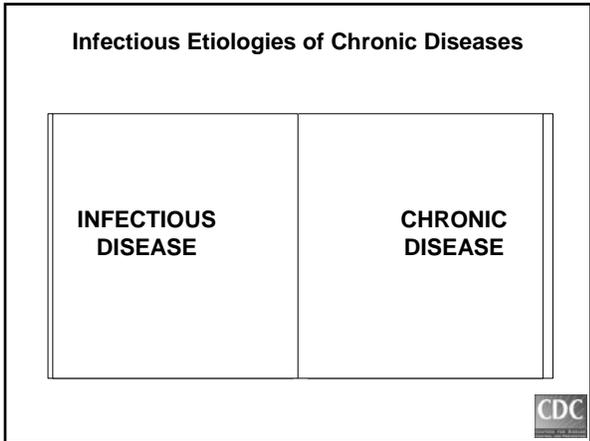
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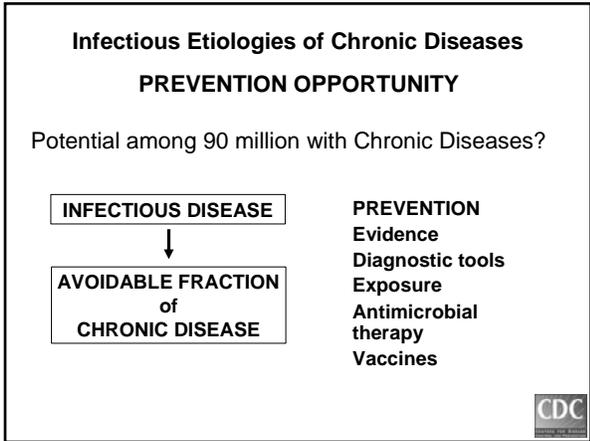
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