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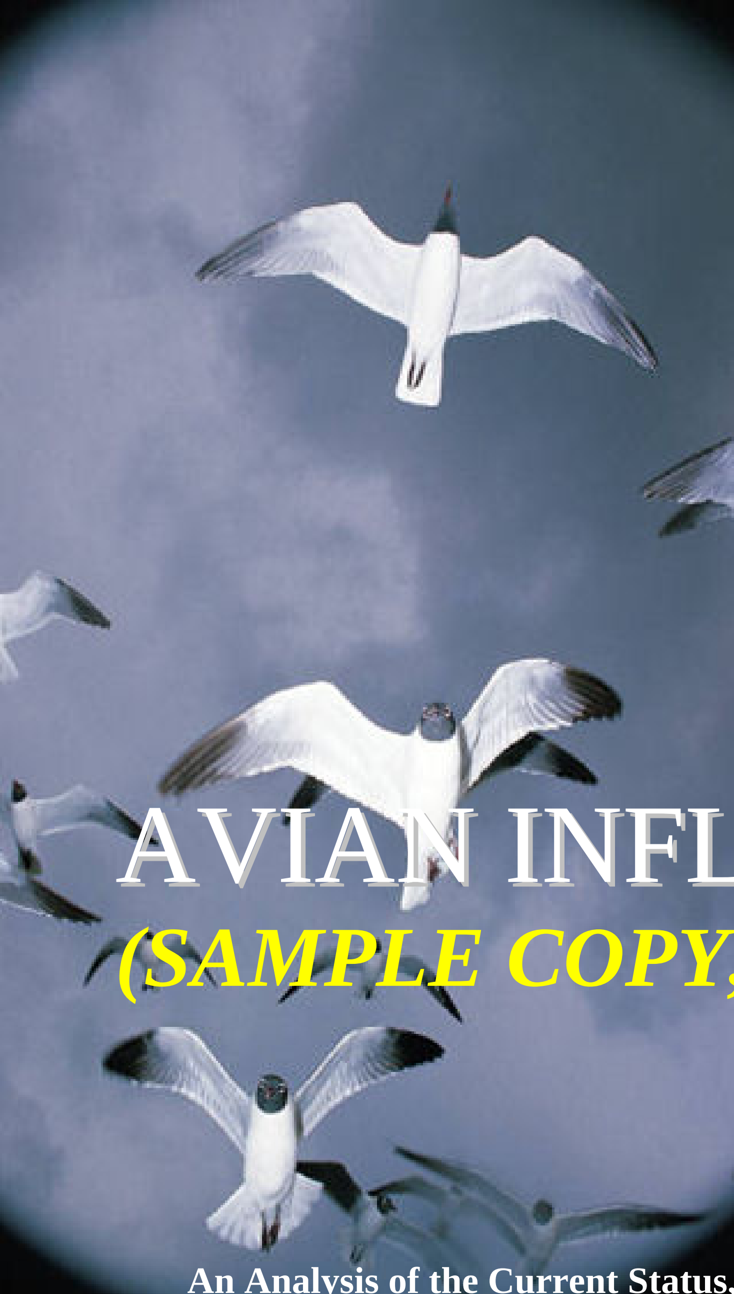

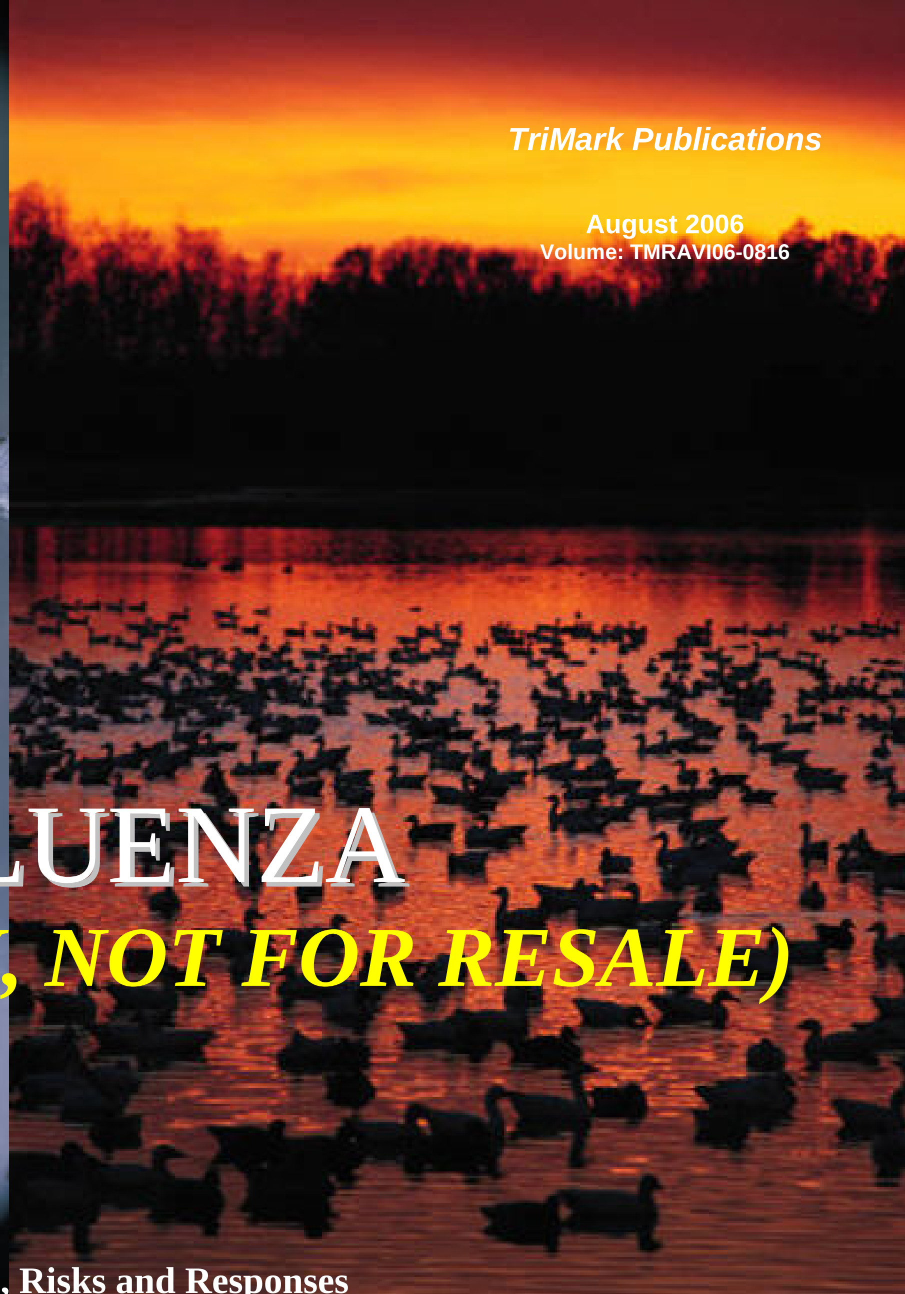

AVIAN INFLUENZA
(SAMPLE COPY, NOT FOR RESALE)

An Analysis of the Current Status, Risks and Responses

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1. Overview

1.1 Statement of Report

The purpose of this report is to understand the current status of avian influenza: its progress, the risks to human populations and the public health response to the crisis. The specific objectives of this analysis are to:

- Examine the epidemiology of avian influenza.
- Describe the diagnosis and treatments available for influenza.
- Discuss preparedness for a worldwide pandemic.
- Evaluate the world economic impact of an influenza epidemic.

1.2 Scope of Report

The U.S., Asia and Europe are the focus of this study. Primary attention is paid to the clinical market segment and, separately, to the medical procedures and supplies for the influenza infection control market. An analysis of the technology trends and developing areas of influenza infection science is provided, along with a review of the market for pharmaceutical agents, vaccines and hospital supplies in clinical use. Activity in research—including the factors that influence infection control—are addressed in this review. Also discussed are changes that have stimulated this disease and patterns of information processing in assessing its spread. Several subjects related to the major elements of influenza treatment such as disposable plastic supplies, needles and lancets are discussed only briefly because they are considered entirely different fields or markets. Fuller explorations of these areas of interest can be found in other TriMark Publications reports such as *Disposable Syringe Markets*, *Disposable Medical Supplies* and *Molecular Diagnostics Markets* at http://www.trimarkpublications.com.

1.3 Objectives

The goal of this report is to review the potential threat of a human influenza pandemic resulting from the avian flu virus. It defines the responses that are now being undertaken worldwide by governmental authorities to contain the spreading bird flu. Specifically, this study contains:

- A comprehensive overview of the several categories of anti-influenza technology platforms that are or will be revolutionizing flu related healthcare in hospitals.
- Full descriptions of the public health measures involved in controlling the spread of avian influenza and the prevention of cross infection to humans.
- Analysis of the technological approaches undertaken by various world governments, as well as industry and end-user response to these ideas.
- Regulatory issues and legislation affecting use and marketing of influenza prevention and treatment products.
- Forecasts for each category of infection control.

The analysis will allow the reader to:

- Evaluate the effect of strategic factors and technology driven measures for controlling avian flu and subsequent human infections.
- Investigate how cost-constraints and technological advances are driving change in the influenza market.
- Examine the structure of the avian flu response across the world and learn how to respond successfully to this challenge to human health.
- Assess the growth opportunities in all influenza-related treatments and preventative measures.
- Review the main approaches in each sector and plan a strategy in line with the strengths and weaknesses of the infection control measures.

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1.4 Methodology

The information made available in this report is based upon a collection of government data made publicly available, as well as trade association reviews and company data. Additional data was obtained from proprietary databases. Moreover, this review is based upon interviews with medical professionals in the infectious disease field. They were queried, some several times, about healthcare strategies as well as their overall thoughts about the possible responses to a flu pandemic. Descriptions of the laboratories and patient facilities were derived from interviews with laboratory directors and medical technologists in these areas. Clinical aspects of influenza treatment and diagnosis were discussed with physicians and clinicians directly involved with patient care.

Other sources of information included trade association publications and meetings, product brochures and catalogs, and company literature. Approaches for responding to an influenza epidemic threat were adapted from recommendations of the World Health Organization (WHO), and guidelines published by the American Family Physicians, and the *Journal of the American Academy of Family Physicians*. Annual reports, 10k filings and financial reports were used as the basis for data reported on publicly held companies.

Finally, some of the information was taken from Biotechnology Associates' databases and from TriMark's private data stores. The information set forth in this study was obtained from sources that we believe to be reliable, but we do not guarantee the accuracy, adequacy or completeness of any information, omission or for the results obtained by the use of such information. TriMark does not guarantee its accuracy, adequacy or completeness of any information, omission or for the results obtained by the use of such information.

1.5 Executive Summary

Influenza, commonly known as the flu, is an infectious disease that infects birds and mammals (primarily of the upper airways and lungs in mammals) and is caused by an RNA virus. Flu rapidly spreads around the world in seasonal epidemics, killing millions of people in pandemic years and hundreds of thousands in non-pandemic years. Three influenza pandemics in the 20th century—each following a major genetic change in the virus—killed millions of people all over the world. The world's current major influenza pandemic threat is H5N1; but it is at present mostly in birds, not in people.

Only influenza A viruses infect birds, and all known subtypes of influenza A viruses can infect birds. However, there are substantial genetic differences between the influenza A subtypes that typically infect birds and those that infect both people and birds. Three prominent subtypes of the avian influenza A viruses that are known to infect both birds and people are H5, H7 and H9.

Influenza viruses are dynamic and are continuously evolving. Influenza viruses can change in two different ways: antigenic drift and antigenic shift. Influenza viruses are changing by antigenic drift all the time, but antigenic shift happens only occasionally. Influenza type A viruses undergo both kinds of changes; influenza type B viruses change only by the more gradual process of antigenic drift. Some relevant facts include:

- Influenza has been causing recurrent epidemics of febrile respiratory disease every [redacted] to [redacted] years for at least [redacted] years.
- Over [redacted] deaths in U.S. per epidemic.
- Over [redacted]% of mortality is in persons aged [redacted] and older.
- Attack rates of [redacted]% to [redacted]% in general population.
- Nursing home attack rates of [redacted]%.
- There is always the potential for pandemics.

During the winter months, influenza is one of the most common illnesses among patients of primary care physicians, with as many as [redacted] in [redacted] adults infected each year. The prevalence of influenza is an important factor to consider. Prevalence varies from less than [redacted]% among patients with febrile respiratory illness before or after the influenza season, to approximately [redacted]% to [redacted]% during the early and late influenza season ("shoulder" season), to [redacted]% or more during the peak of influenza season. The proportion of patients with influenza A versus influenza B varies each year, as does the seasonal peak. For example, in the 2004-2005 flu season, the peak occurred in mid-February; [redacted]% of patients with suspected influenza were diagnosed with the illness, and approximately one third of these patients had

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influenza B. During the 2003-2004 flu season, however, the peak occurred in mid-December, and although [redacted]% of patients with suspected influenza were diagnosed with the disease, only [redacted]% had influenza B.

The U.S. Centers for Disease Control and Prevention (CDC) releases annual guidelines for the prevention of influenza and the appropriate use of antiviral agents. The cost-effectiveness of empiric treatment with antiviral agents for appropriate patients with influenza is high. Oseltamivir (Tamiflu) therapy is recommended for all patients during a regional epidemic when the probability of influenza is over [redacted]%. Treatment is also recommended with amantadine (Symmetrel), rimantadine (Flumadine), or oseltamivir when the likelihood of influenza is high.

Domesticated birds may become infected with avian influenza virus through direct contact with infected waterfowl or other infected poultry, or through contact with surfaces (such as dirt or cages) or materials (such as water or feed) that have been contaminated with virus. People, as well as inanimate objects such as vehicles and bird cages, can be vectors for the spread of influenza virus from one farm to another. When this happens, avian influenza outbreaks can occur among poultry.

Influenza A viruses have infected many different animals, including ducks, chickens, pigs, whales, horses and seals. However, certain subtypes of influenza A virus are specific to certain species—except for birds—which are hosts to all known subtypes of influenza A. Subtypes that have caused widespread illness in people either in the past or currently are H3N2, H2N2, H1N1 and H1N2. H1N1 and H3N2 subtypes also have caused outbreaks in pigs, and H7N7 and H3N8 viruses have caused outbreaks in horses. Although avian influenza A viruses usually do not infect humans, the WHO reports more than [redacted] confirmed cases of human infection with avian influenza viruses since [redacted]. However, experts at WHO and elsewhere believe that the world is now closer to another influenza pandemic than at any time since [redacted], when the last of the previous century's three pandemics occurred.

A practical strategy for avian influenza involves using parallel assays:

- Influenza A/B real-time assay (M1 and NS1 targets).
- CDC subtype-specific real-time assays, H1, H3, H5 and H7 (HA target).
- Conventional PCR sub-typing assay (H1, H3, H5).
- Culture when H5N1 ruled-out.

Preparing for a pandemic requires the leveraging of all instruments of national power, as well as coordinated action by all segments of government and society. Influenza viruses do not respect the distinctions of race, sex, age, profession or nationality, and are not constrained by geographic boundaries. The next pandemic is likely to come in waves, each lasting months, and pass through communities of all size across the world.

U.S. national strategy will provide a framework for future U.S. government planning efforts that is consistent with the national security strategy and the national strategy for homeland security. It recognizes that preparing for and responding to a pandemic cannot be viewed as a purely federal responsibility, and that the nation must have a system of plans at all levels of government and in all sectors outside of government that can be integrated to address the pandemic threat.

The continuing outbreaks that began in late 2003 and early 2004 have been disastrous for the poultry industry in Asia; by mid-2005, more than [redacted] birds had died or been destroyed and losses to the poultry industry are estimated to be in excess of USD $[redacted]. There are two main categories of economic impacts associated with outbreaks of infectious diseases such as HPAI in poultry and a potential human influenza pandemic:

- Costs of sickness or death resulting from the disease outbreaks.
- Costs associated with public and private efforts to prevent the emergence or spread of the disease and to treat its effects.

The most direct impact on output would be through the effect of increased illness and mortality on the size and productivity of the world labor force. In addition, there will also be a general decline in labor productivity due to illness and sick leave among the labor force at large. Such productivity losses due to illness during normal annual influenza episodes are estimated to be ten times as large as all other flu-related costs combined. Other long-term impacts would play out as the increased costs of preventing and treating disease reduced savings and investment.

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The impact on output at the national level would vary widely, depending on the extent of the epidemic, the country's demographic structure, the extent of unemployed resources and other key variables.

A severe pandemic would reduce the labor force. In [redacted], the U.S. labor force totaled [redacted] people. Under the assumption of an attack rate of [redacted]% and a case fatality rate of [redacted]%—the same assumptions applied to the population as a whole—a severe pandemic would cause the deaths of more than one million labor force participants, or about [redacted]% of the labor force. Since growth in the labor force averaged [redacted]% during the 1948-2005 period, losing [redacted]% of the labor force would be equivalent to a pause of [redacted] year in the growth of the U.S. workforce. Under the assumptions for infection and mortality associated with the mild-pandemic scenario—an attack rate of [redacted]% and a fatality rate of just over [redacted]%—the number of workers killed would be [redacted], or [redacted]% of the labor force.

Only two antiviral drugs, oseltamivir and zanamivir, have shown promise in treating avian influenza. Oseltamivir is licensed as Tamiflu and manufactured under patent by the Swiss firm Roche Laboratories in tablet form. A treatment course for Tamiflu includes ten pills taken over five days. Zanamivir is licensed as Relenza and manufactured by GlaxoSmithKline. Relenza is administered by oral inhalation and is not recommended for people with chronic lung problems. The U.S. Food and Drug Administration (FDA) has approved both antiviral drugs for treating influenza. Tamiflu has also been approved to prevent influenza infection.

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