Microbial control in Asia: A bellwether for the future?

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Abstract

Advances and barriers faced by microbial control efforts in Asia offer instructive insights for microbial control in general. The papers in this series, which are based on plenary lectures given at the Society for Invertebrate Pathology 2006 meeting in Wuhan, China, explore the history and current status of microbial control in China, Japan, and Southeast Asia, and in doing so, bring to light the following key assumptions that deserve further examination; (1) the adoption rate of microbial control is well documented; (2) microbial control agents can compete directly with conventional insecticides; (3) microbial control agents are relatively easy and inexpensive to produce and develop; (4) patents will promote innovation and investor interest in microbial control. Alternative viewpoints are presented that can hopefully aid in future efforts to develop more safe and effective microbial control agents.

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1. Introduction

The sheer size of the Asian continent—spreading over 44 million square kilometers and containing over half of the world’s population—makes attempts to characterize it almost impossible. Even when the perspective is narrowed down to an overview of microbial control in the region, the spectrum of information available for synthesis is enormous, and bursting with paradox, as the papers in this series demonstrate. It is in Asia after all, or China to be specific, where the first records of insect diseases, dating back to the seventh century B.C., were found (Tanada and Kaya, 1993), but it is also in Asia where some of the newest advances in pathogen discovery, genetics, and biotechnology are occurring today. It is in Asia, and particularly in Thailand and India, where labor-intensive, non-commercial on-farm production systems for microbial control agents have been widely developed, but it is also in Asia—in China and Thailand particularly, where insect pathogens are commercially produced using capital-intensive systems that rely on the most current advances in industrial fermentation technology. It is in Asia where the science of preventing insect diseases in silkworm colonies has, at various times in history, been at least as important as the science of disseminating diseases of insects for the purpose of biological control, and it is in Asia where products based on both naturally occurring and genetically engineered microbes share the marketplace. Amidst all of this diversity, though, a desire for alternatives to conventional pest control unites the people of this region, whether they are the rural subsistence farmers of Cambodia who struggle to produce enough food to survive, or the affluent urban consumers of Beijing and Tokyo, who want to buy organic produce in their supermarkets.

The task of describing some of the history, state of current affairs and also the future challenges for microbial control in Asia is a formidable one, but one that the authors of the following series of papers have dealt with expertly. There are unexpected insights to be gained when comparing the three vastly different approaches to microbial control presented in this series—from China’s large, government-financed, centralized, and highly industrialized effort to Japan’s smaller, privatized industry to Southeast Asia’s emphasis on localized production systems. Despite these differences, many of the same economic, cultural,
and political factors contribute to the success or failure of microbial control projects in each region. Comparing the experiences described in these papers also challenges some of our key assumptions about microbial control—assumptions so firmly entrenched that we may not always know that we are even making them. For the remainder of this overview, then, I would like to highlight some of those assumptions and suggest some alternative viewpoints that will hopefully further efforts to identify more safe and effective microbial control agents in the future.

2. Assumption 1: The adoption rate of microbial control is well documented

2.1. Sales in Europe and North America

Ideally, any evaluation of the current state of affairs of microbial control should be based on an understanding of where, by whom and how frequently it is used around the world. Unfortunately, the information we have available to us is fragmented, at best. The most detailed documentation available is based on estimates of sales of biopesticide (commercial microbial control agents) products in Europe and North America (Fig. 1), and even in these cases, we are dealing with rough approximations. And when we move away from Europe and North America, there are tremendous gaps in information. The good news, is that from the little that can be uncovered, it appears that the $200 million in sales that was achieved in Europe and North America in 2004 (Fig. 1) is only a fraction of the total use of microbial control. Non-commercial uses of microbial control, as well as sales outside of North America and Europe, although unquantified, appear to constitute an equal, if not a larger component.

2.2. Global sales

In terms of sales of commercial products outside of Europe and North America, we know from Dafang Huang et al.’s article (2007) that there are more than 300 microbial control products registered in China today, with $40 million alone worth of Bacillus thuringiensis (Bt) products sold in 2001. And in Japan, there are over $9 million (US) in sales of biopesticides each year, as described in Yasuhisa Kunimi’s review (2007). In countries such as India, Thailand, Brazil, South Africa, and others, sales figures for microbial control agents are significant, but unquantified. These data are difficult to track for several reasons: many biopesticides are produced by very small regional companies whose existence is barely noted by market surveys; larger companies may import microbial control products and then re-package them under a dizzying variety of names; and perhaps most importantly, there has been no concerted effort to even begin the process of tracking global sales of biopesticides.

2.3. Documenting non-commercial uses

The effort of documenting the use of microbial control agents is further complicated by the difficulty of obtaining any quantitative data on their non-commercial uses. This is frustrating, because some of microbial control’s greatest successes have come in non-commercial, donor or government-funded projects such as control of Candian forestry pests with Bt subsp. kurstaki, of African locusts with Metarhizium or of rhinoceros beetles in Asia and the Pacific and Indian Ocean Islands with the Oryctes virus (Gelernter and Lomer, 2000). Non-commercial uses of microbial control may represent some of the most important opportunities for its use—opportunities where it can contribute to the alleviation of poverty, environmental damage or pesticide poisonings. But as long as we fail to characterize these non-commercial uses, we cannot easily learn from, or build on these valuable experiences.

But where to start? There is of course no sales data to collect, and if any data on the extent of use is obtained (which it rarely is), it is measured in units of pounds of material applied (essentially a meaningless value, since the weight of a microbial control agent does not necessarily equate with its activity, and is not easily converted into other units) or hectares treated (a preferable measurement, but still not easily compared against sales data). In one of the few non-commercial scenarios that have been well documented, Cuban authorities have tracked the output of 220 government funded, small biocontrol factories that produce Beauveria and Bt, as well as predators and parasitoids, and distribute them free of charge to farmers. In 2002, it is estimated that approximately 1 million hectares of Cuban agriculture were under biocontrol using these materials (Nicholls et al., 2002). Although Cuba’s heavily nationalized economy and relative isolation from the rest of the world makes their demand for alternative pest con-
trols more extreme than in most countries, their example demonstrates the potential for non-commercial applications of microbial control, and indicates that it is much more widely used than sales figures alone tell us.

2.4. The need for quantification, and who needs to do it

Without some way of measuring the use of microbial control agents, how can we understand what works, what doesn’t work, or why? After all of the work that researchers put into discovering, characterizing, and testing microbial control agents, why is so little done to follow up on their adoption (a series of papers on microbial control in Asia by Grzywacz (2003) are among the few that attempt this task)? And if this is an important task, whose job is it to implement it? For commercial products, it is unwise to depend exclusively upon companies to provide this information; while they may document their own sales, they are not always inclined to share this information publicly, and in addition, do not have reliable figures for other companies. Surveys conducted by market research companies (Evans, 2005) or by trade associations such as the International Biocontrol Manufacturers Association (IBMA) are the best source of information currently available, but they tend to ignore portions of the world outside of Europe and North America. And for non-commercial uses, the situation is even worse, because there are not even product sales figures available to track.

For all of these reasons, it is important to seriously consider how this data can be generated, shared, and stored in the future. At a minimum, applications for applied microbial control grants should include a section on use patterns and/or adoption of the microbial control agent in question. Agricultural economists should be consulted for advice on design and collection of this type of data, and industry organizations such as IBMA should be contacted for assistance. Ultimately, a web-based clearinghouse for storage and sharing of this important information, along the lines of the Bt toxin nomenclature website (Crickmore et al., 2005), should be considered. However, none of this is likely to occur unless microbial control researchers themselves are willing to take leadership on this issue.

3. Assumption 2: Microbial control agents can compete directly with conventional insecticides

3.1. Another look at expectations

As detailed elsewhere (Gelernter, 2005), tremendous optimism about the potential for microbial control was fueled starting around 1980, when a Bt toxin was first expressed in Escherichia coli (Schnepf and Whitely, 1981). Armed with the belief that genetic engineering and/or more strategic discovery programs would yield microbial control products that could directly compete with conventional pesticides, companies, and investors, primarily in North America, created a whirlwind of activity and hope that lasted about 15 years, until the mid-1990s. During this time, over 20 new companies in the US alone became involved in the development of microbial pesticides while many others sprang up around the world, patent offices were besieged with new applications for microbial control applications, and investors began clamoring to cash in on the promise of agricultural biotechnology. It was typical at that time for companies to expect that each new product could earn a minimum of $10 million per year, and that biopesticides would be able to compete directly with chemical insecticides in major commodity markets (such as corn, cotton or soybeans) in addition to the niche markets (forestry, organic agriculture) where they were already well accepted.

The growth of organic agriculture (Fig. 2, Table 1), an increase in the number of cases of pesticide resistance (Georghiou, 1990) as well as several food safety scares (Carlson, 1989) gave more support to the assumption that demand for alternative pest control products would grow rapidly during this time. But despite gradually increasing use (Fig. 1), commercial sales of biopesticides never made the quantum leap that had been widely expected, and by 1995, many companies had dropped or severely cut back on their efforts to develop microbial control products (Gelernter, 2004).

3.2. Performance issues

There are several reasons that the optimistic expectations of the 1980s and 1990s were not met, and the first is of course related to performance—both in terms of field efficacy and in terms of the high costs of development and production. While there certainly have been advances made in the insecticidal activity of microbial control agents, those advances have been incremental, rather than transforma-

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**Fig. 2.** Growth of organic agriculture in 15 European Union countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, UK), 1985–2004 (Lampkin, 2004). These countries accounted for approximately 20% of the world’s 24 million hectares of organic agriculture in 2004 (Willer and Yussefi, 2004).
tive. And while manufacturing efficiencies have been accomplished, most biopesticides are still more expensive to produce than their conventional chemical counterparts. At this point in our history, the limitations posed by living organisms with specific host ranges and inefficient delivery systems are simply too significant to be dramatically overridden, even through genetic manipulation or discovery of new microbial isolates. Instead, the successes that were hoped for with microbial control agents have come to phenomenal fruition in the development of transgenic Bt crops (Fig. 3). The use of a crop, rather than a microbe, to deliver the Bt toxin proved to be the technological advance that has led to impressive insect control efficacy, worldwide adoption and high corporate profits. In Asia, adoption of Bt crops—primarily cotton—has grown rapidly, with 7.5 million hectares of Bt cotton and corn (40% of the global total) planted in 2006 (James, 2006).

If this situation sounds grim for microbial control agents, it is only so when viewed in light of expectations that were more widely optimistic than they were based on an understanding of the biology of microorganisms. An honest evaluation of the benefits and limitations of microbial control agents—at least as they currently perform—should lead to periodic re-evaluations of the expectations that we have for them. And based on what we know of microbial control agents today, their greatest chances for success still occur in situations where their benefits (human and environmental safety, unique mode of action, specificity) outweigh their limitations. For the most part, these are niche or specialty markets or developing world applications that are ignored by larger agrichemical companies because of their smaller market sizes or lack of profit potential. The opportunities to compete on a direct basis with conventional pesticides in large commodity markets are still almost always limited to cases where resistance to chemical pesticides has developed or where environmental, regulatory or legal restrictions are placed on the use of chemical pesticides.

3.3. Safer products from an unexpected source: The agrichemical industry

Some of the same concerns about pest resistance and environmental and human safety that have driven the adoption of microbial control have also driven agrichemical companies to develop new products with “softer” environmental and human safety profiles. As a result, many of the situations in which microbial control had formerly been a “natural” fit have been threatened by adoption of products that share many of the same positive safety features, but that also have the benefits of broad host spectra, stability and ease of use that are typical of conventional insecticides. It is interesting to note that many of the products that compete most directly with microbial control agents are themselves derived from microorganisms themselves. These include Bt transgenic crops as well as several new insecticide products that are based on microbial fermentation products (Table 2).

4. Assumption 3: Microbial control agents are relatively easy and inexpensive to produce and develop

One of the most appealing features of microbial control agents is that, unlike conventional chemical pesticides, many of them can be manufactured using relatively simple and inexpensive technologies and materials. For example, baculoviruses and entomopathogenic nematodes can be produced in vivo in insects, while fungi such as Beauveria and Metarhizium can be grown on sterilized grains. This feature lends itself well to the appealing concepts of local

Table 1
Organic agriculture in Asia (Willer and Yussefi, 2004)

<table>
<thead>
<tr>
<th>Country</th>
<th># organic hectares</th>
</tr>
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<tbody>
<tr>
<td>China</td>
<td>301,295</td>
</tr>
<tr>
<td>Ukraine</td>
<td>239,542</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>177,700</td>
</tr>
<tr>
<td>Indonesia</td>
<td>40,000</td>
</tr>
<tr>
<td>India</td>
<td>37,050</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>36,882</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>15,215</td>
</tr>
<tr>
<td>Vietnam</td>
<td>6475</td>
</tr>
<tr>
<td>Japan</td>
<td>5083</td>
</tr>
<tr>
<td>Thailand</td>
<td>3993</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>2540</td>
</tr>
<tr>
<td>Pakistan</td>
<td>2009</td>
</tr>
<tr>
<td>Philippines</td>
<td>2000</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>902</td>
</tr>
<tr>
<td>Laos</td>
<td>150</td>
</tr>
<tr>
<td>Nepal</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>870,881</td>
</tr>
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Of the more than 24 million hectares that are managed organically worldwide, Asian organic agriculture (including grazing, crop and aquaculture) accounted for 3.7% in 2004. (Willer and Yussefi, 2004).
production and distribution of biocontrol agents, as well as to the establishment of small, entrepreneurial microbial control companies. But as Ole Skovmand’s paper in this series (2007) describes, production is only one part of the role that manufacturing companies must fulfill. Prevention of problems such as microbial contamination, low potency formulations, attenuation of insecticidal activity or physical deterioration of the formulated product are equally important, and many small-scale operations are simply not equipped with the expertise, the materials, and equipment or the capital to cope. As a result, the quality of products produced by small, under funded production facilities has been erratic, giving first time users no incentive for repeat applications. This problem has been especially prevalent in the developing world (Jenkins and Grzywacz, 2000; Skovmand, 2007), but has also been documented in small production facilities in the developed world (Gaugler et al., 2000). Larger manufacturing facilities struggle with these same issues as well, but are more likely to have the funds available to address them.

If it is the case that production of high quality microbial control agents is more capital and knowledge-intensive than previously believed, what are the implications? For donor and government agencies or for entrepreneurs who are starting up new manufacturing projects, there must be an acknowledgement that financial support of a production facility entails not only the initial costs of construction and equipment, but also ongoing quality control training for staff members, as well as purchase of the tools necessary to evaluate and test for product quality. In some cases, the overhead involved in operating a small facility may be prohibitive, and it may be more efficient to fund fewer and larger facilities. Another inescapable conclusion is that high quality microbial control agents are not cheap to produce, a fact that further limits their profitability and commercial attractiveness.

An even larger cost that must be considered is the cost of developing a new microbial control agent. When activities such as discovery, strain improvement, laboratory and field testing, regulatory fees, and tests, formulation development and farmer education are tallied, fees typically exceed $25 million (US) for a single product. Yet despite its magnitude, this cost has been frequently overlooked by granting agencies, researchers, and even some companies. The reason for what seems to be a case of such embarrassing ignorance is that until quite recently, public agencies subsidized the majority of development costs, based on their assessment that microbial control was a “common good” that was worth subsidizing (Gelernter, 2005).

5. Assumption 4: Patents will promote innovation and investor interest in microbial control

The passage of laws such as the Bayh-Dole Act of 1980 (Kennedy, 2005) made it possible, for the first time, for publicly funded research institutions to patent their discoveries and to exclusively license them to private companies for a fee. Soon afterwards came the first reports that insect pathogens such as Bt could be genetically engineered (Schneppf and Whitely, 1981). Taken together, these events resulted in a rush for universities and government agencies to patent their researchers’ discoveries, for companies to clamor for exclusive licenses to them, and for those same companies to aggressively pursue their own patent estates. Now, more than 25 years after the passage of Bayh-Dole, the advantages and disadvantages of patenting microbial control technologies are far from clear. On the one hand, a survey of microbial control products currently on the market reveals that almost none are protected by patents. Instead, the overwhelming majority is based on organisms that are in the public domain—either discovered by university or government researchers before 1980, or if discovered afterwards, not patented. The most commonly employed proprietary approach for today’s microbial control products exists in the form of trade secrets—procedures (usually in manufacturing or formulation) that are not patented, but are protected from use by competitors by keeping their details a closely held secret within a given company. Based on an examination of currently available microbial control products, then, patents do not appear to have played a role in development of new products. It is likely that the relatively small markets and relatively high costs of producing biopesticides has made companies shy away from the burden of additional investment in fees for the lawyers, licenses, and ongoing patent defense activities that would be involved. Universities and government agencies that have nevertheless continued to patent their microbial control discoveries have found few, if any of their inventions licensed to private companies.

The situation is very different for Bt transgenic crops—products that are direct descendants of microbial control agents. Here, there are hundreds of patents, from both private and public entities, that cover everything from the procedure by which the Bt DNA is moved into plants to specific Bt genes. With a global market that was estimated at $6.15 billion (US) in 2006 (James, 2006), the companies involved clearly believe that their investment in creating and defending their patent estates is worthwhile. But ques-

Table 2

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Company</th>
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<tbody>
<tr>
<td>Abamectin</td>
<td>Syngenta</td>
</tr>
<tr>
<td>Bifenazate</td>
<td>Uniroyal</td>
</tr>
<tr>
<td>Chloronicotinyls</td>
<td>Syngenta, Bayer, Arysta</td>
</tr>
<tr>
<td>Harpins</td>
<td>Eden Bioscience</td>
</tr>
<tr>
<td>Polyoxin D</td>
<td>Cleary Chemical</td>
</tr>
<tr>
<td>Pymetrozine</td>
<td>Syngenta</td>
</tr>
<tr>
<td>Spinosad</td>
<td>Dow</td>
</tr>
<tr>
<td>Spiromesifen</td>
<td>Bayer</td>
</tr>
</tbody>
</table>

Note that most of these products are based on metabolites of microbial fermentations and that most are marketed by major agrichemical companies.
tions have recently been raised about the barriers that such patents place on humanitarian uses of patented technologies as well as on the conduct and availability of publicly funded research results (Boettiger and Bennett, 2006; Gonzalez, 2006). For example:

- If a discovery addresses a non-commercial use or a low profitability use in a small niche market, will a patent limit its development because licensing fees are out of proportion to the commercial value?
- In the event that a discovery is patented, what procedures are available to allow researchers from different institutions to collaborate on further development of the technology?
- If a discovery has large commercial potential (such as a Bt gene for use in transgenic plants), will a patent limit its use in situations where the gene has little or no commercial value, but significant humanitarian value for use in subsistence or specialty crops?
- If a discovery is not patented, how will researchers and the institutions they work for be rewarded for their years of effort and expense?

In response to these questions, a variety of new approaches to the question of intellectual property have been proposed. While most deal with higher stakes technologies such as transgenic crops, there are applications for microbial control that are worth considering as well.

5.1. The open science movement

There is a growing movement is calling for researchers in the biological sciences to consider the Open Source Software concept as a model for addressing their own intellectual property concerns (Gonzalez, 2006). Open Source Software is developed by making a software program’s source code publicly available so that it can be freely modified and disseminated, thus ensuring sharing of information and more rapid development of new innovations. Any improvements or modifications made to the original source code must also be made publicly available. At the same time, the software developer’s innovations are still protected by an open source license and they are still free to charge for their programs, if they wish.

Leading the effort to translate these principles into applications that are useful in the biological sciences is the non-profit organization CAMBIA. To facilitate the type of scientific exchange that it believes is necessary for continued progress in agricultural research, CAMBIA provides free access to technologies developed by their staff for either research or commercial application. (CAMBIA’s portfolio of technologies includes Transbacter, a system for transforming plant cells, that is presented as an alternative to the patented systems now used by companies who market transgenic crops). An open science license—known as the Biological Open Source license—is required, however, before the technologies are shared, and the licensee must agree to share their data on any improvements that are made to the system. While this effort is still in its infancy, and while there are many unanswered questions about the applicability of open source software procedures to the biological sciences, the approach is appealing and is fomenting additional solutions, many of which are complimentary to the open source concept. To help researchers avoid getting trapped in the “patent thicket”, CAMBIA also provides useful databases of worldwide patents, patent applications, patent status information, and data on patent law around the globe.

5.2. The public sector intellectual property resource for agriculture (PIPRA)

Public sector institutions may patent promising technologies and license them to private companies, but should retain rights to use their discoveries in subsistence and specialty crop (small market) scenarios when they issue commercial licenses. In addition, these institutions need to widely share their discoveries with one another to form a collective intellectual property management framework. These ideas have been put forward by the “Public Sector Intellectual Property Resource for Agriculture” (PIPRA), a recently formed group of universities, foundations and non-profit research institutions (Atkinson et al., 2003). The organization has developed a series of position papers and internet-based resources for scientists who share these concerns.

5.3. Science Commons

The Science Commons concept was introduced in 2005 to explore ways in which the barriers created by the pursuit of intellectual property can be addressed and the public good can be better served (Garlick, 2005). To do this, innovative approaches to technology licensing (“open licensing”) and to sharing of scientific data (through open access journals that are free of charge, and also free of most copyright and licensing restrictions) have been proposed.

6. Conclusions: Microbial control as a “common good”

The history and implementation of microbial control in Asia illustrates many of the opportunities and also many of the challenges that this field faces in the future. As detailed here and in the following three papers, the increased demand for safer pest control products, more experience in manufacturing and implementation of microbial control strategies, and improved dissemination of information through international exchange and through the internet all enhance the prospects for continued adoption of microbial control. But unreasonable expectations for performance, inappropriate regulatory guidelines, lack of documentation on the uptake of microbial control strategies, difficulties in implementing local production schemes and inhibition of
scientific exchange due to limitations imposed by patents need to be dealt with.

It is clear from this list of challenges that future efforts will require support—in the form of cooperation from regulatory agencies, in the form of data exchange from private and public institutions, and in the form of financial support from granting agencies and donor organizations. The assumption that microbial companies can support the bulk of the research and development effort is unrealistic, as most of these companies are relatively small and have modest operating budgets. Instead, microbial control needs to be defined for what it is—as a “common good”—that although it may have low value to traditional investors, has a high value to society because of its environmental and human safety, its ability to uniquely address pest control problems, its contribution to the development of related products and its role in enhancing our understanding of the biological world around us. Continued progress in this field is therefore largely a public sector responsibility, and one that is well worth the investment.

Acknowledgments

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