北京智飞绿竹生物制药有限公司
Beijing Zhifei Lvzhu Biopharmaceutical Co., Ltd.

Development on Shigella Vaccine

Dr. Lin Du

www.vaccine.com.cn

Disease background

Dr. Kiyoshi Shiga
Discoverer of the Dysentery Bacillus
1898

Bulletin of the World Health Organization, 1999, **77** (8)

Global burden of *Shigella* infections: implications for vaccine development and implementation of control strategies

K.L. Kotloff,[1] J.P. Winickoff,[2] B. Ivanoff,[3] J.D. Clemens,[4] D.L. Swerdlow,[5] P. J. Sansonetti,[6] G.K. Adak,[7] & M.M. Levine[8]

Few studies provide data on the global morbidity and mortality caused by infection with *Shigella* spp.; such estimates are needed, however, to plan strategies of prevention and treatment. Here we report the results of a review of the literature published between 1966 and 1997 on *Shigella* infection. The data obtained permit calculation of the number of cases of *Shigella* infection and the associated mortality occurring worldwide each year, by age, and (as a proxy for disease severity) by clinical category, i.e. mild cases remaining at home, moderate cases requiring outpatient care, and severe cases demanding hospitalization. A sensitivity analysis was performed to estimate the high and low range of morbid and fatal cases in each category. Finally, the frequency distribution of *Shigella* infection, by serogroup and serotype and by region of the world, was determined.

The annual number of *Shigella* episodes throughout the world was estimated to be 164.7 million, of which 163.2 million were in developing countries (with 1.1 million deaths) and 1.5 million in industrialized countries. A total of 69% of all episodes and 61% of all deaths attributable to shigellosis involved children under 5 years of age. The median percentages of isolates of *S. flexneri, S. sonnei, S. boydii,* and *S. dysenteriae* were, respectively, 60%, 15%, 6%, and 6% (30% of *S. dysenteriae* cases were type 1) in developing countries; and 16%, 77%, 2%, and 1% in industrialized countries. In developing countries, the predominant serotype of *S. flexneri* is 2a, followed by 1b, 3a, 4a, and 6. In industrialized countries, most isolates are *S. flexneri* 2a or other unspecified type 2 strains.

Shigellosis, which continues to have an important global impact, cannot be adequately controlled with the existing prevention and treatment measures. Innovative strategies, including development of vaccines against the most common serotypes, could provide substantial benefits.

Disease background

Lancet Infect Dis 2017;
17: 909–48
Published Online
June 1, 2017

Articles

Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015

*GBD Diarrhoeal Diseases Collaborators**

Findings Globally, in 2015, we estimate that diarrhoea was a leading cause of death among all ages (1·31 million deaths, 95% uncertainty interval [95% UI] 1·23 million to 1·39 million), as well as a leading cause of DALYs because of its disproportionate impact on young children (71·59 million DALYs, 66·44 million to 77·21 million). Diarrhoea was a common cause of death among children under 5 years old (499 000 deaths, 95% UI 447 000–558 000). The number of deaths due to diarrhoea decreased by an estimated 20·8% (95% UI 1
Rotavirus was the leading cause of diarrhoea deaths (199 000, 95% UI 165 000–241
(164 300, 85 000–278 700) and *Salmonella* spp (90 300, 95% UI 34 100–183 100). Among
three aetiologies responsible for the most deaths were rotavirus, *Cryptosporidium* spp, a
in safe water and sanitation have decreased diarrhoeal DALYs by 13·4%, and reductio
have decreased diarrhoeal DALYs by 10·0% between 2005 and 2015.

In 2015, estimates 2.39 billion diarrhoea episodes that cause 1.31 million deaths in the world, the leading pathogens were:

Rotavirus： 199 thousands
Shigella ： 164 thousands
Salmonella： 90 thousands

Disease background

1991
Graduated from school and as a member of shigella vaccine R&D Group in LIBP

1991年度全国甲、乙类传染病疫情的初步分析

中国预防医学科学院流研所流行病室

Incidence of Notifiable Infectious Disease in 1991 in China

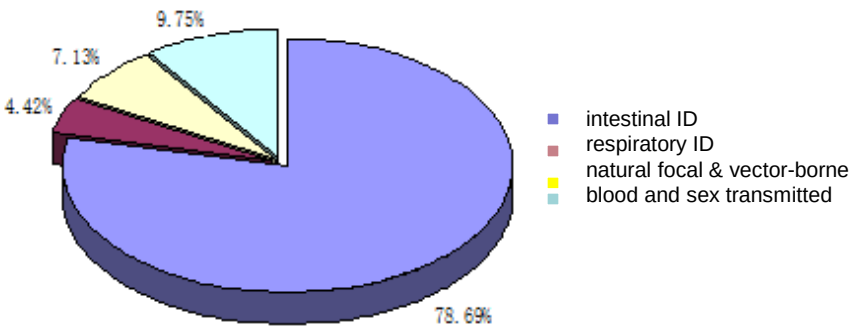
1991年全国24种甲、乙类法定报告传染病的发病和死亡构成

病名		发病数	占总发病数构成(%)	死亡数	占总死亡数构成(%)
呼吸道传染病	麻疹	108 291	3.58	262	3.59
	百日咳	9 706	0.32	19	0.26
	白喉	229	0.01	40	0.55
	流脑	7 087	0.23	412	5.64
	猩红热	28 849	0.95	21	0.29
	小计	154 156	5.09	754	10.23
肠道传染病	霍乱	205	0.01	0	0
	肝炎(未含乙型肝炎)	970 807	32.13	580	7.94
	痢疾	1 242 814	41.14	861	11.79
	伤寒副伤寒	110 257	6.65	235	3.23
	脊髓灰质炎	1 715	0.06	35	0.48
	小计	2 325 798	76.99	1 711	23.44
传播	乙型肝炎	273 203	9.04	436	5.97
	艾滋病	0	0	0	0
	淋病	71 623	2.37	0	0
	梅毒	726	0.02	0	0
	小计	345 552	11.43	436	5.97

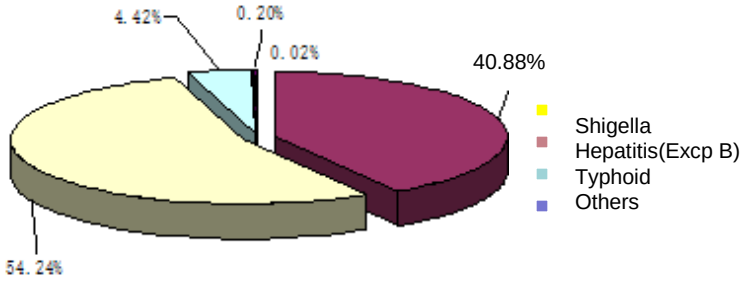
Shigella:
Incidents: 1.24millions; Proportion:41.14%;Rank No. 1
Deaths : 861; Proportion:11.79%;Rank No. 1

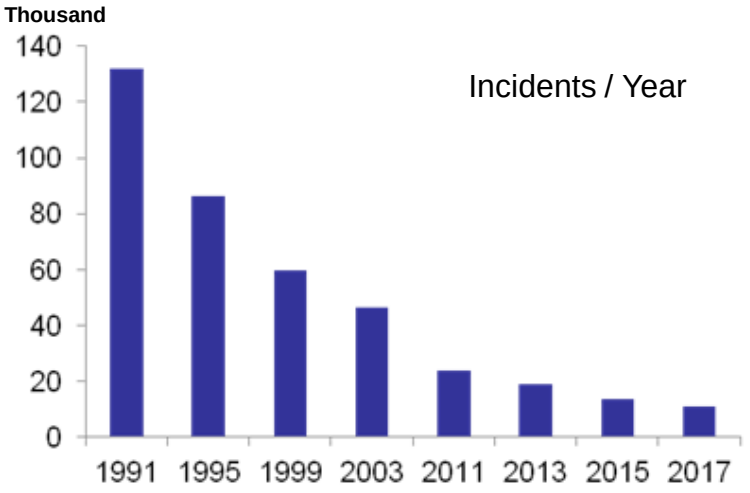
Disease background

Percentage of infectious diseases in China in 1990

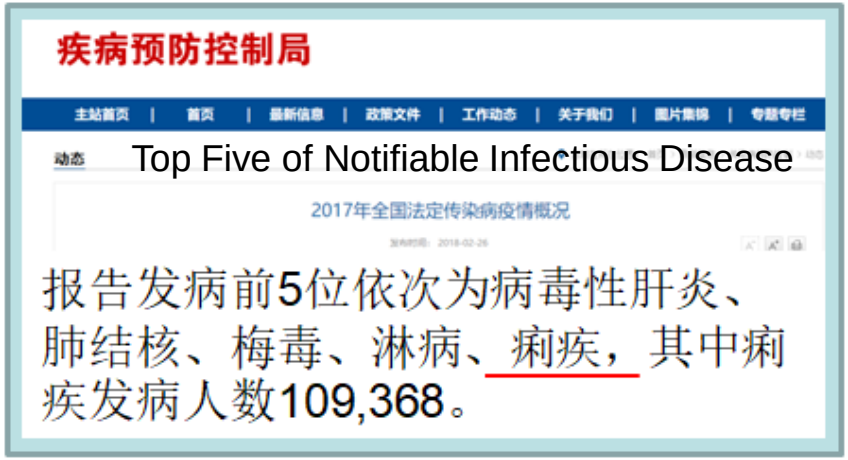


Percentage of enteric infectious diseases in China in 1990





Incidents / Year



Top Five of Notifiable Infectious Disease

Disease background

Ages (Year)	<5	5~14	>14
Incident Rate （%）	2.5	0.3	0.6

Am. J. Trop. Med. Hyg., 73(2), 2005, pp. 416–422

OCCURRENCE OF SHIGELLOSIS IN THE YOUNG AND ELDERLY IN RURAL CHINA: RESULTS OF A 12-MONTH POPULATION-BASED SURVEILLANCE STUDY

XUAN-YI WANG,* LIN DU, LORENZ VON SEIDLEIN, ZHI-YI XU, YING-LIN ZHANG, ZHI-YONG HAO, OAK-PIL HAN, JING-CHEN MA, HYE-JON LEE, MOHAMMAD ALI, CHANG-QUAN HAN, ZHAN-CHUN XING, JI-CHAO CHEN, AND JOHN CLEMENS

International Vaccine Institute, Seoul, South Korea; Department of Molecular Virology, Shanghai Medical College, Fudan University, Shanghai, People's Republic of China; Lanzhou Vaccine Institute, Lanzhou, People's Republic of China; Center for Disease Control and Prevention of Zhengding County, Shijiazhuang, Hebei Province, People's Republic of China

Abstract. In 2002, population- and treatment center–based surveillance was used to study the disease burden of shigellosis in rural Hebei Province in the People's Republic of China. A total of 10,105 children with diarrhea or dysentery were enrolled. Infants were treated most frequently for diarrhea (1,388/1,000/year) followed by children ≤ 5 years old (618/1,000/year). Shigellosis was treated most often in children 3–4 years old (32/1,000/year) and people > 60 years of age (7/1,000/year). Fifty-six percent (184 of 331) *Shigella* isolates were detected in patients who had non-bloody diarrhea. *Shigella flexneri* was identified in 93% of 306 isolates. The most common *S. flexneri* serotypes were 1a (34%), X (33%), and 2a (28%). More than 90% of the *Shigella* isolates were resistant to cotrimoxazole and nalidixic acid, but remained susceptible to ciprofloxacin, norfloxacin, and gentamicin. Widespread resistance to antibiotics adds urgency to the development and use of vaccines to control shigellosis.

Disease background

·疾病与卫生监测·

广西钟山县细菌性痢疾流行病学监测研究

李建标[1]，黎芝[1]，潘斌[2]，龚健[3]，李翠云[3]，施礼威[3]，黄英[4]，杜琳[5]

1.贺州市疾病预防控制中心，广西 542899；2.钟山县疾病预防控制中心；3.广西壮族自治区疾病预
4.北京思睦瑞科医药信息咨询有限公司；5.北京智飞绿竹生物制药有限公司

摘要：目的 建立细菌性痢疾流行病学监测系统，为开展痢疾疫苗临床研究奠定科学基础。**方法** 201
2015年11月以广西钟山县发病率较高的5个乡镇为监测区域、6月龄～6岁为监测人群，采用被动监测和
结合的监测手段，对就诊与未就诊的腹泻病例均采集粪便标本/肛拭子，进行志贺菌分离培养鉴定，阳性
方复核。从当地统计局收集监测初期和末期的常住人口信息。依据病原学诊断结果计算发病率，分析流
果 监测人群20 300人中监测到腹泻患者1 247例，确诊细菌性痢疾病例205例，发病率为1 00 9.85/10万。各乡镇发病率为661.38/10万～1 461.89/10万，差异有统计学意义（P=0.001）。发病时间主要在6～11月，7月为高峰；各年龄组发病差异有统计学意义（P=0.000），以1岁组最高（2 474.89/10万）；性别差异无统计学意义。志贺菌属4个菌群均检出，以宋内（D群）为绝对优势菌群（196例，占95.61%）。**结论** 在钟山县建立的细菌性痢疾流行病学监测系统获得了较为客观、真实的发病数据，为痢疾疫苗保护效果的临床研究设计提供了科学依据。

关键词：细菌性痢疾；流行病学；监测

中图分类号：R 516.41 **文献标识码：**A **文章编号：**1673-758X(2018)03-0220-03

2014.11~2015.10, 20300 children age 6 months~6 years were passitive surveillance for shigella diseases, 1247 diarrhea samples were collected, 205 were culture positve for the pathogen, the incident rate was 1.0%, the highest was in children 1 years old, the incident rate was 2.47%.

Vaccine background

Whole cells inactive vaccine

Streptomycin dependent

T32

EcSf

SFL

SC

CVD

WRS

S-WC

Conj

FS

FSM

FSW

NaConj

Sythetic

BioConj

Outer Mumbrane

1940s

1960s

1980-2000s

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Vaccine. 2010 Mar 2;28(10):2231-5. doi: 10.1016/j.vaccine.2009.12.050. Epub 2010 Jan 5.

Age-related efficacy of Shigella O-specific polysaccharide conjugates in 1-4-year-old Israeli children.

Passwell JH[1], Ashkenzi S, Banet-Levi Y, Ramon-Saraf R, Farzam N, Lerner-Geva L, Even-N… R; Israeli Shigella Study Group.

Collaborators (51)

71.1% protection for 3~4 years old

THE LANCET

Double-blind vaccine-controlled randomised efficacy trial of an investigational *Shigella sonnei* conjugate vaccine in young adults

Dani Cohen, Shai Ashkenazi, Manfred S Green, Michael Gdalevich, Guy Robin, Raphael Slepon, Miri Yavzori, Nadav Orr, Colin Block, Isaac Ashkenazi, Joshua Shemer, David N Taylor, Thomas L Hale, Jerald C Sadoff, Danka Pavliakova, Rachel Schneerson, John B Robbins

Summary

Background The aim of this double-blind randomised vaccine-controlled trial was to assess the efficacy of a conjugate vaccine composed of *Shigella sonnei* O-specific polysaccharide bound to *Pseudomonas aeruginosa* recombinant exoprotein A (*S sonnei*-rEPA) and of an oral, live-attenuated *Escherichia coli*/*S flexneri* 2a (EcSf2a-2) hybrid vaccine among military recruits in Israel at high risk of exposure to *Shigella* spp. We report here our preliminary findings on the efficacy of *S sonnei*-rEPA; we have not documented sufficient cases to assess the efficacy of EcSf2a-2.

Methods Between April, 1993, and August, 1994, male Israeli military recruits aged 18–22 years were asked to take part in our study. We enrolled 1446 soldiers from seven separate field sites (groups A–G). Soldiers were randomly allocated one oral placebo injection of meningococcal oral placebo *S flexneri* 2a were the control group. We defined a *S sonnei* shigellosis diarrhoea with a positive faecal culture for *S sonnei*. Each group of soldiers was followed up for 3·5–7·0 months. The primary endpoint was protective efficacy of *S sonnei*-rEPA against *S sonnei* shigellosis.

Findings Cases of culture-proven *S sonnei* shigellosis occurred in four groups of soldiers (groups A–D), which comprised 787 volunteers (312 received *S sonnei*-rEPA, 316 received EcSf2a-2, and 159 received meningococcal control vaccine). In groups A–C, cases of shigellosis occurred 70–155 days after vaccination, whereas in group D cases occurred after 1–17 days. In groups A–C, the attack rate of shigellosis was 2·2% in recipients of *S sonnei*-rEPA compared with 8·6% in controls (protective efficacy 74% [95% CI 28–100], p=0·006). *S sonnei*-rEPA also showed significant protection against shigellosis in group D (43% [4–82], p=0·039). Prevaccination and post-vaccination ELISA measurements of antibody to *S sonnei* lipopolysaccharide among recipients of *S sonnei*-rEPA showed that the vaccinees who developed *S sonnei* shigellosis had significantly lower serum IgG and IgA responses to the homologous lipopolysaccharide than those who did not (p=<0·05).

Interpretation One injection of *S sonnei*-rEPA confers type-specific protection against *S sonnei* shigellosis. The high antibody concentration induced by the conjugate vaccine in volunteers who did not develop shigellosis suggests that there is an association between serum antibody titre and protection.

Lancet 1997; **349**: 155–59

Introduction

dysentery in children, which leads to arrested growth for several months after the disease.[3] The low inoculum required to cause related shigellosis (100–1000 organisms)[4] facilitates the transmission of the disease, and explains the frequent failure of adequate sanitary and hygienic measures to prevent shigellosis. Strict attention to handwashing after defaecation and measures to control houseflies have been shown to reduce the incidence of shigellosis under artificially controlled conditions.[5] However, such measures are difficult to implement. Furthermore, antibiotic treatment of shigellosis is not always successful, because isolates are increasingly resistant to antimicrobial agents.[6] For these reasons, WHO has assigned a high priority to the development of vaccines for shigellosis.

There is no licensed vaccine against shigellosis. Although the nature of immunity against the disease is little understood, there is evidence that infection with shigellae confers type-specific immunity of limited duration to lipopolysaccharide (LPS),[7,8] which supports the O-polysaccharide as protective antigen. Case-control and prospective studies of shigellosis among soldiers of the Israel Defence Force have shown a significant correlation between pre-existing type-specific serum concentrations of IgG antibody to shigella LPS and resistance to shigellosis.[9,10] On the basis of these observations, we proposed that serum IgG anti-LPS may confer protection against the disease.[10] Conjugates of shigella O-specific polysaccharides have been developed because they have the potential to elicit high serum concentrations of LPS antibodies.[11] Previous phase I and II studies among soldiers in the US Army and Israel Defence Force

74% Protective Rate
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Registered in “ClinicalTrials.gov” from 2005

25 items → Screened out (Same/Terminated) → **11 Projects**

Vaccine	Sponsor	Phase	Kinds	Updata	
WRS	PATH	Ⅰ	Oral-atten	2018.01	
SC599	Pasteur	Ⅱ	Oral-atten	2006.09	3
sf2a1208s	PATH	Ⅱb	Oral-Inac	2012.12	
Conj	NICHD	Ⅲ	NaConj	2008.01	
OSPC/rBRU	NICHD	Ⅰ	NaConj	2013.04	
Bi-Conj	Lvzhu	Ⅰ	NaConj	2018.06	6
SF2a-TT15	Pasteur	Ⅰ	Sythetic	2017.06	
Flexyn2a	Limma	Ⅱb	BioConj	2016.09	
GVXNSD133	GlycoVaxyn	Ⅰ	BioConj	2010.10	
1970GAHB	GSK	Ⅱb	Outer-M	2018.08	2
Invaplex	AMRMC	Ⅱb	Outer-M	2009.07	

Vaccine background

福氏 2a 痢疾结合疫苗临床安全性和免疫原性观察

双价痢疾结合疫苗的安全性及免疫原性

口服痢疾双价活疫苗 FS 胶囊安全性观察

口服福氏 2a 和宋内氏痢疾双价活疫苗 FS 的双盲对照现场观察

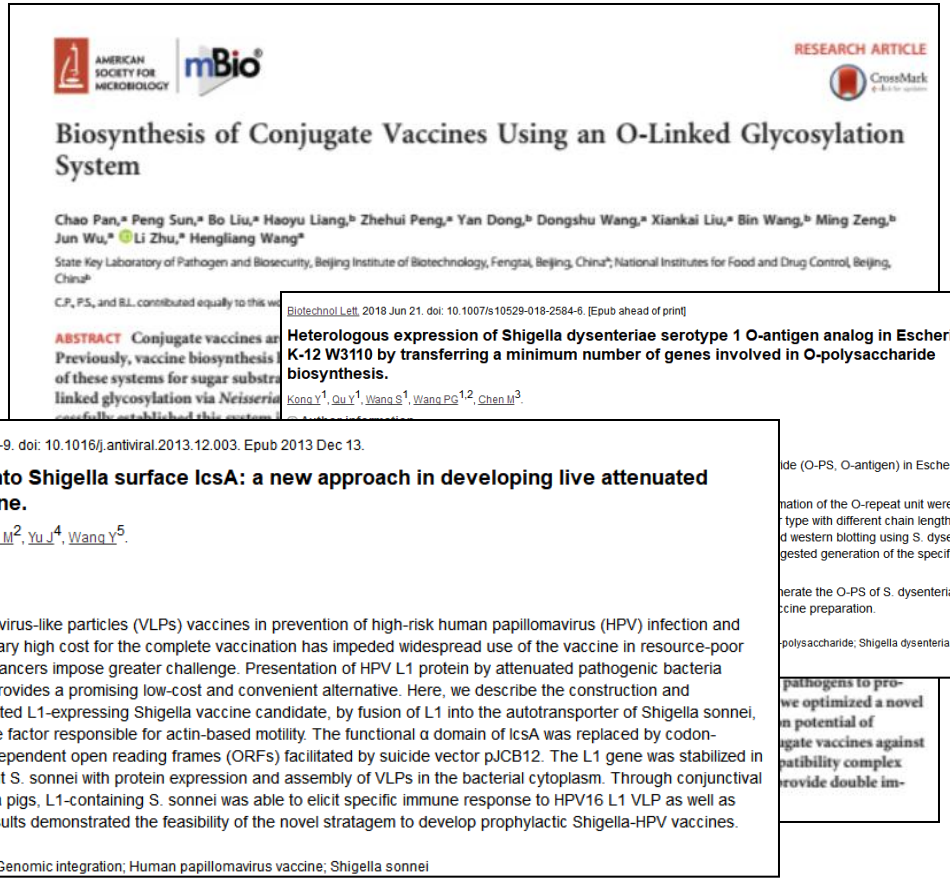
福氏和宋内氏痢疾双价杂交菌苗株 FSM21-17 人体试验观察

痢疾杆菌福氏 2a *sf*301*DsbA*/*virG* 双突变减毒活候选疫苗构建和初步鉴定

There were many studies on Shigella vaccine in China around 2000, mainly focusing on oral vaccines, two of them got new drug certificates.

Vaccine background

After 2010, only 3 papers on shigella vaccine could be searched, all in phase of preliminary conceptual verification in laboratory.



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RESEARCH ARTICLE

Biosynthesis of Conjugate Vaccines Using an O-Linked Glycosylation System

Chao Pan,[a] Peng Sun,[a] Bo Liu,[a] Haoyu Liang,[b] Zhehui Peng,[a] Yan Dong,[b] Dongshu Wang,[a] Xiankai Liu,[a] Bin Wang,[b] Ming Zeng,[b] Jun Wu,[a] Li Zhu,[a] Hengliang Wang[a]

State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Biotechnology, Fengtai, Beijing, China[a]; National Institutes for Food and Drug Control, Beijing, China[b]

C.P., P.S., and B.L. contributed equally to this wo

ABSTRACT Conjugate vaccines ar
Previously, vaccine biosynthesis
of these systems for sugar substra
linked glycosylation via *Neisseria*

Biotechnol Lett. 2018 Jun 21. doi: 10.1007/s10529-018-2584-6. [Epub ahead of print]

Heterologous expression of Shigella dysenteriae serotype 1 O-antigen analog in Escherichia coli K-12 W3110 by transferring a minimum number of genes involved in O-polysaccharide biosynthesis.

Kong Y[1], Qu Y[1], Wang S[1], Wang PG[1,2], Chen M[3].

ide (O-PS, O-antigen) in Escherichia coli by

nation of the O-repeat unit were introduced
type with different chain lengths of O-
d western blotting using S. dysenteriae 1
gested generation of the specific S.

herate the O-PS of S. dysenteriae 1 and
ccine preparation.

-polysaccharide; Shigella dysenteriae 1

pathogens to pro-
we optimized a novel
n potential of
gate vaccines against
patibility complex
rovide double im-

Antiviral Res. 2014 Feb;102:61-9. doi: 10.1016/j.antiviral.2013.12.003. Epub 2013 Dec 13.

Fusion of HPV L1 into Shigella surface IcsA: a new approach in developing live attenuated Shigella-HPV vaccine.

Xu D[1], Wang D[2], Yang X[3], Cao M[2], Yu J[4], Wang Y[5].

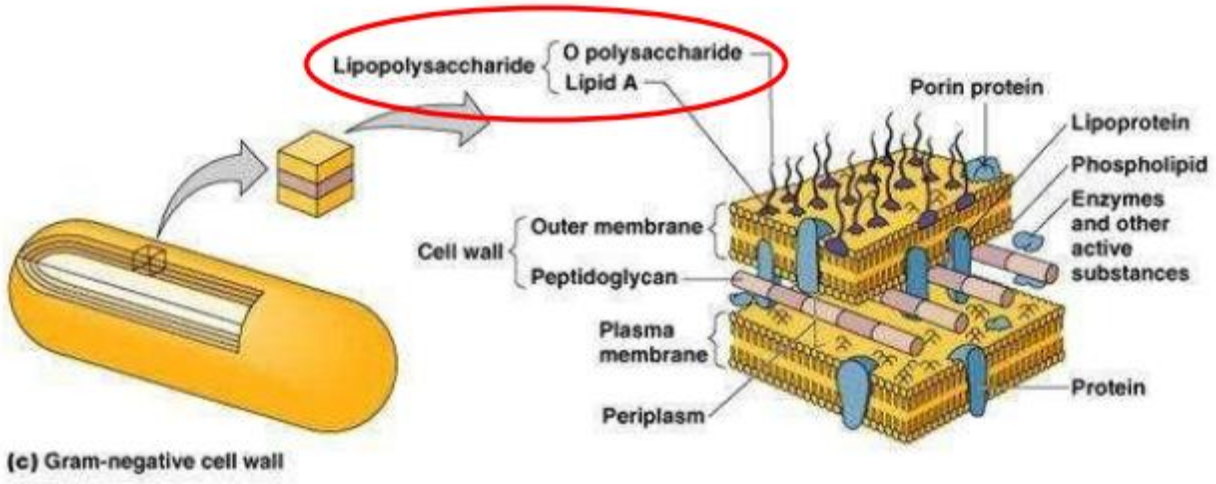
Author information

Abstract

Despite the success of L1 virus-like particles (VLPs) vaccines in prevention of high-risk human papillomavirus (HPV) infection and cervical cancer, extraordinary high cost for the complete vaccination has impeded widespread use of the vaccine in resource-poor countries, where cervical cancers impose greater challenge. Presentation of HPV L1 protein by attenuated pathogenic bacteria through natural infection provides a promising low-cost and convenient alternative. Here, we describe the construction and characterization of attenuated L1-expressing Shigella vaccine candidate, by fusion of L1 into the autotransporter of Shigella sonnei, IcsA, an essential virulence factor responsible for actin-based motility. The functional α domain of IcsA was replaced by codon-optimized L1 gene with independent open reading frames (ORFs) facilitated by suicide vector pJCB12. The L1 gene was stabilized in the genome of recombinant S. sonnei with protein expression and assembly of VLPs in the bacterial cytoplasm. Through conjunctival route vaccination in guinea pigs, L1-containing S. sonnei was able to elicit specific immune response to HPV16 L1 VLP as well as bacterial antigens. The results demonstrated the feasibility of the novel stratagem to develop prophylactic Shigella-HPV vaccines.

KEYWORDS: Autotransporter; Genomic integration; Human papillomavirus vaccine; Shigella sonnei

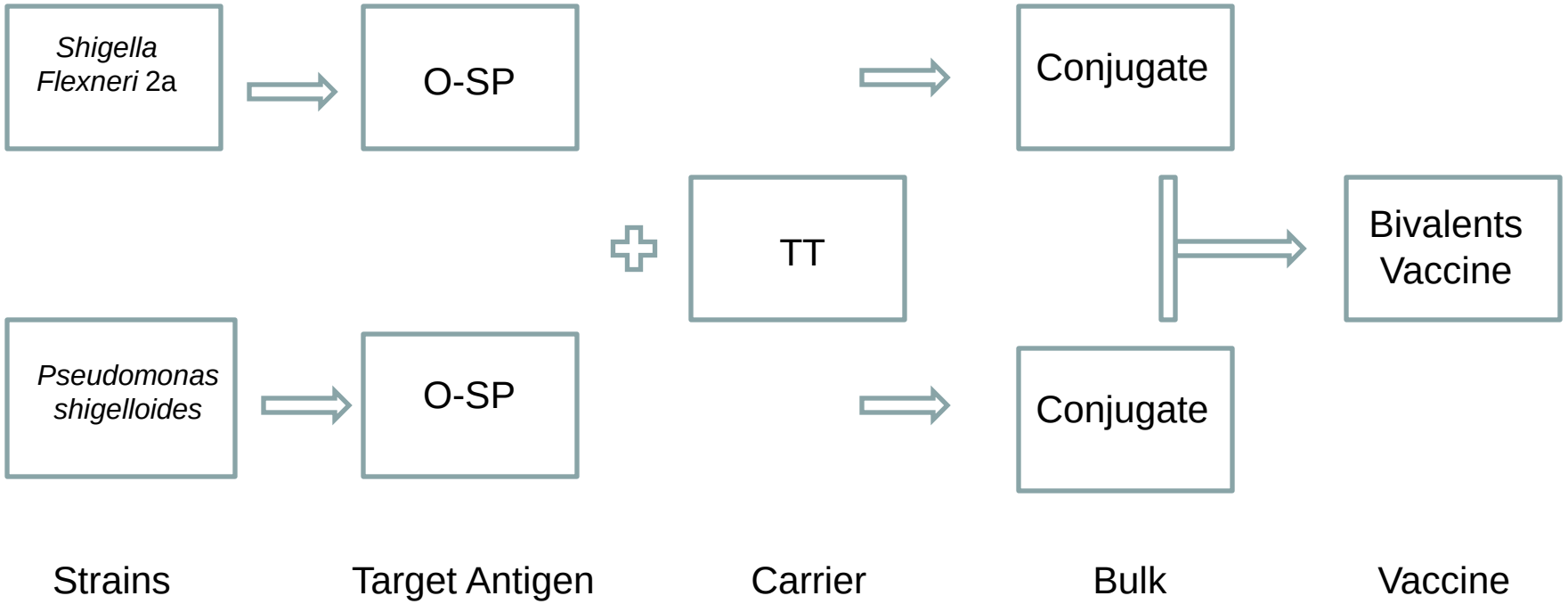
Bivalent Shgella Conjugate Vaccine



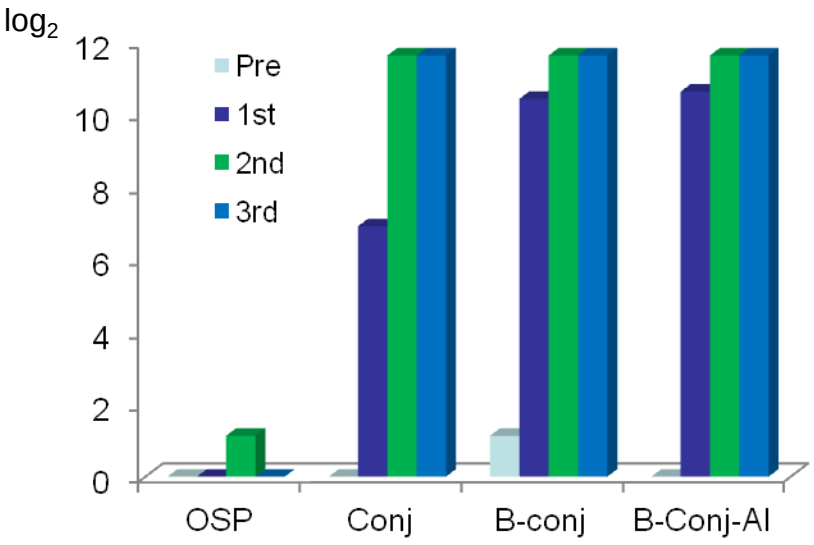
LPS of Gram-negative Bacteria

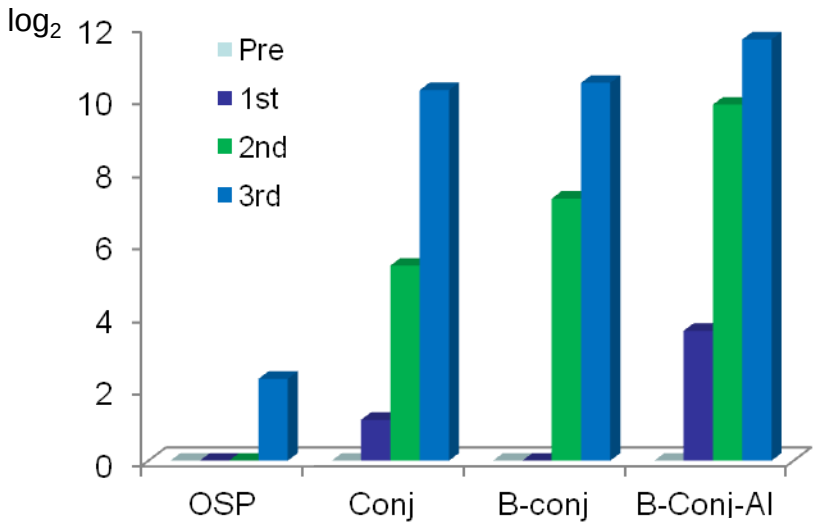
O-sp link with carrier protein to form Conjugate

Bivalent Shgella Conjugate Vaccine



Specific antibody response in mice with different antigen





	Group
OSP	O-sp
Conj	Conjugate
B	Bivalent Conjugate
B-Al	Bivalent Conjugate with Al

Bivalent Shgella Conjugate Vaccine

Investigators

Study Chair: Du lin, Master Beijing Zhifei Lvzhu Biopharmaceutical Co., Ltd

More Information

Responsible Party: Beijing Zhifei Lvzhu Biopharmaceutical Co., Ltd
ClinicalTrials.gov Identifier: NCT03561181 History of Changes
Other Study ID Numbers: [illegible]
First Posted: June 19, 2018 Key Record Dates
Last Update Posted: June 19, 2018
Last Verified: June 2018

Sponsor:
Beijing Zhifei Lvzhu Biopharmaceutical Co., Ltd

Information provided by (Responsible Party):
Beijing Zhifei Lvzhu Biopharmaceutical Co., Ltd

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description

Brief Summary:
The purpose of this study is to evaluate safety of S.flexneriza-S.sonnei Bivalent Conjugate Vaccine in healthy volunteers aged above 3 M

Condition or disease	Intervention/treatment
Dysentery Dysentery, Bacillary	Biological: S.Flexneriza-S.Sonnei Bivalent Conjugat

Study Design

Study Type: Interventional (Clinical Trial)
Estimated Enrollment: 180 participants
Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: None (Open Label)
Primary Purpose: Prevention
Official Title: A Single-center, Open, Phase I Clinical Trial to Evaluate Safety of S.Flexneriza-S.Sonnei Bivalent Conjuga
Actual Study Start Date: July 18, 2017
Actual Primary Completion Date: January 28, 2018
Estimated Study Completion Date: July 1, 2018

Phase Ⅰ Clinical Trial

A total of 180 healthy volunteers were recruited and evenly distributed into 9 groups:

Group	Age	No. Subjects	Dose Amount	No. Injections	Remarks
1	≧18 Years	20	Full dose	1	
2	6-17 Years	20	Half dose	1	
3		20	Full dose	1	
4	1-5 Years	20	Half dose	1	
5		20	Full dose	1	
6	6-11 Months	20	Half dose	2	1 month apart for each injection
7		20	Full dose	2	
8	3-5 Months	20	Half dose	3	
9		20	Full dose	3	
Total		180			

Active safety surveillance was conducted for 1 month after each injection. The vaccine was administered in age descending schedule after safety reports reviewed in the older groups.

Adverse reaction 30 mins after each injection

Adverse reaction（1st injection）

	3-5(h)	3-5(f)	6-11(h)	6-11(f)	1-5(h)	1-5(f)	6-17(h)	6-17(f)	>18
Total	1	1	1	1	1	1	0	0	1
Systemic	1	1	1	1	1	1	0	0	1
Fever	1	1	1	1	1	1	0	0	1

* All were mild

Adverse reaction（2nd injection）

	3-5(h)	3-5(f)	6-11(h)	6-11(f)
Total	0	1	0	4
Systemic	0	1	0	4
Fever	0	1	0	4

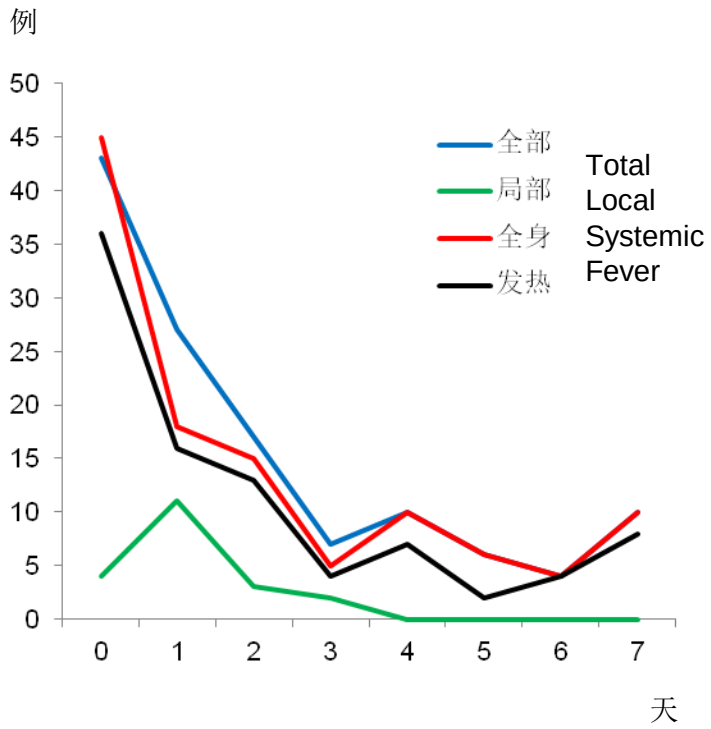
* All were mild

Adverse reaction（3rd injection）

	3-5(h)	3-5(f)
Total	3	1
Systemic	3	1
Fever	3	1

- h-group：2 cases were mild；1 was moderate
  F-group：1 case was severe

Adverse reaction in 7 days



		3-5(h)	3-5(f)	6-11(h)	6-11(f)	1-5(h)	1-5(f)	6-17(h)	6-17(f)	>18	合计
0天	全部（人）	6	8	6	9	2	2	2	4	4	43
	局部（次）	0	0	0	0	1	0	1	0	2	4
	全身（次）	6	12	7	10	1	2	1	4	2	45
	发热（次）	6	7	5	9	1	2	1	3	2	36
1天	全部（人）	6	4	4	4	2	0	4	2	1	27
	局部（次）	1	1	2	1	2	0	2	2	0	11
	全身（次）	6	4	1	3	0	0	3	0	1	18
	发热（次）	5	4	1	3	0	0	3	0	0	16
2天	全部（人）	4	1	4	2	4	0	1	0	1	17
	局部（次）	2	0	0	0	0	0	1	0	0	3
	全身（次）	3	1	4	2	4	0	0	0	1	15
	发热（次）	3	0	3	2	4	0	0	0	1	13
3天	全部（人）	2	2	1	1	0	0	0	0	1	7
	局部（次）	1	0	0	0	0	0	0	0	1	2
	全身（次）	1	2	1	1	0	0	0	0	0	5
	发热（次）	1	1	1	1	0	0	0	0	0	4
4天	全部（人）	3	3	2	1	1	0	0	0	0	10
	局部（次）	0	0	0	0	0	0	0	0	0	0
	全身（次）	3	3	2	1	1	0	0	0	0	10
	发热（次）	3	2	1	1	0	0	0	0	0	7
5天	全部（人）	1	1	0	3	0	0	0	1	0	6
	局部（次）	0	0	0	0	0	0	0	0	0	0
	全身（次）	1	1	0	3	0	0	0	1	0	6
	发热（次）	0	1	0	1	0	0	0	0	0	2
6天	全部（人）	0	0	1	0	2	0	0	1	0	4
	局部（次）	0	0	0	0	0	0	0	0	0	0
	全身（次）	0	0	1	0	2	0	0	1	0	4
	发热（次）	0	0	1	0	2	0	0	1	0	4
7天	全部（人）	3	2	1	3	1	0	0	0	0	10
	局部（次）	0	0	0	0	0	0	0	0	0	0
	全身（次）	3	2	1	3	1	0	0	0	0	10
	发热（次）	3	1	1	2	1	0	0	0	0	8

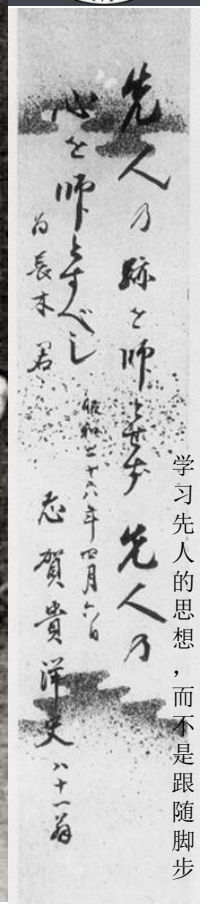
Phase Ⅱ clinical Trial

1050 subjects were divided into different groups. Blood samples were collected before and 1 month after immunization. Specific antibody levels were measured to analyze the effects of doses, injections and adjuvant necessity.

Vaccine	Age group			
	3-5 M (3 injection)	6-11 M (2 injection)	1-5 Y (1 injection)	1 -5 Y (2 Injections)
Bivalent Vaccine (Half dose)	100	100	100	/
Bivalent Vaccine (Full dose)	100	100	100	100
Vaccine Control (Full dose, No Adjuvant)	/	100	100	/
Hib	50	50	50	/
Total	250	350	350	100

1936年，在哈佛300年庆典上，志贺发言道：痢疾菌的发现搅动着我年轻的心，希望能消灭这种疾病……每年仍有成千上万的患者，曾经闪亮的希望之光就像夏夜的梦一样褪色。圣火不可熄灭。

In 1936, as a senior scientist and honored guest at the tercentenary celebration at Harvard University, Dr. Kiyoshi Shiga began his address as follows: “The discovery of the dysentery bacillus stirred my young heart with hopes of eradicating the disease…Many thousands still suffer from this disease every year, and the light of hope that once burned so brightly has faded as a dream of a summer night. This sacred fire must not burn out”



Dr. Kiyoshi Shiga, 1871–1957

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The Biologics Company
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谢 谢 ！

THANK YOU!

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